Petition

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In the Supreme Court of the United States

OCTOBER TERM, 1981

UNITED STATES OF AMERICA, PETITIONER

v.

GENERIX DRUG CORPORATION, ET AL.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE ELEVENTH CIRCUIT

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QUESTION PRESENTED

Whether a prescription drug product—even though potentially unsafe or ineffective—is exempt from the requirement of premarketing approval by FDA merely because it contains the same active ingredient as another drug that has received FDA approval or that is generally recognized as safe and effective.*

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* In addition to respondent Generix Drug Corporation, the defendants in the district court were Lewis Michael Orlove, Gary R. Dubin, and Ofelia Perez, all of whom were officers or employees of Generix.

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PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE ELEVENTH CIRCUIT

The Solicitor General, on behalf of the United States, petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Eleventh Circuit in this case.[1]

OPINIONS BELOW

The opinion of the court of appeals (App. A, *infra*, 1a-15a) is reported at 654 F.2d 1114. The decision of the district court (App. C, *infra*, 18a-31a) is reported at 498 F. Supp. 288.

JURISDICTION

The judgment of the court of appeals (App. B, *infra*, 16a-17a) was entered on September 4, 1981. On November 24, 1981, Justice White extended the time within which to file a petition for a writ of certiorari to and including January 2, 1982. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

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[1] This case was decided by Unit B of the Fifth Circuit which, on October 1, 1981, became the Eleventh Circuit.

STATUTES INVOLVED

The relevant statutory provisions are set forth in App. E, *infra*, 33a-44a.

STATEMENT

1. Section 505(a) of the Federal Food, Drug, and Cosmetic Act ("the Act"), 21 U.S.C. 355(a), prohibits any person from introducing into interstate commerce any "new drug" that has not been approved by the Food and Drug Administration (FDA).[2] The term "new drug" is defined in Section 201(p) of the Act, 21 U.S.C. 321(p), to mean any drug that is not "generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof," or has not been used to a material extent or for a material time under other than experimental conditions. 21 U.S.C. 321(p).[3]

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[2] The authority to approve new drugs, granted by statute to the Secretary of Health and Human Services, has been delegated to the Commissioner of Food and Drugs, 21 C.F.R. 5.10(a)(1); see 46 Fed. Reg. 26052 (1981). The introduction or delivery for introduction into interstate commerce of an unapproved new drug in contravention of 21 U.S.C. 355 is made a "prohibited act" by 21 U.S.C. 331(d). Violations of 21 U.S.C. 331 may be enjoined under 21 U.S.C. 332. Persons who violate 21 U.S.C. 331 also are subject to criminal penalties (21 U.S.C. 333) and drugs that fail to comply with 21 U.S.C. 355 may be seized and condemned (21 U.S.C. 334). See *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 612-613 (1973); *Ciba Corp.* v. *Weinberger*, 412 U.S. 640, 644 (1973).

[3] A drug may be excluded from 21 U.S.C. 321(p) if it comes within one of the grandfather provisions of that section, not relevant here.

Generix Drug Corporation (Generix) sells generic prescription drugs in interstate commerce—*i.e*, drugs that purport to be copies of brand name or "pioneer" drugs manufactured by other companies. While the "active" ingredients of these generic drugs purport to be identical to those contained in the pioneer drugs, the "inactive" ingredients (*e.g.*, coatings, binders) known as excipients, differ. Many of the generic drugs distributed by Generix had not been approved by the FDA, and in the government's view were "new drugs" within the meaning of the Act. Accordingly, on November 29, 1979, the United States filed an action in the United States District Court for the Southern District of Florida against Generix and several of its officers and employees. The complaint requested both preliminary and permanent injunctive relief.[4]

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[4] The unapproved new drugs distributed by respondents included "Goldline" products containing the following active ingredients: allopurinol, spironolactone, spironolactone with hydrochlorothiazide, furosemide, chlorothiazide with reserpine, amitriptyline with perphenazine, diethylpropion hydrochloride, prochlorperazine maleate, and chlorthalidone (R. 28 n.3). The request for injunctive relief to prevent distribution of unapproved new drugs was not, however, limited to those particular drugs (*ibid.*).

The complaint alleged also that defendants were violating the Act by holding for sale and distributing in interstate commerce drugs that were adulterated within the meaning of 21 U.S.C. 351(a)(2)(B) because of failure to conform to current good manufacturing practices as set forth in 21 C.F.R. Part 211. This petition raises no issue concerning the good manufacturing practices allegations.

"R." refers to the district court record as transmitted to the court of appeals. "Tr." refers to the transcript of the hearing in the district court on the government's motion for a preliminary injunction.

Generix did not deny that the particular drug products referred to in the complaint have not been approved by FDA.[5] The hearing on the government's motion for a preliminary injunction focused, therefore, on the question whether the generic drugs distributed by Generix were "new drugs" within the meaning of 21 U.S.C. 321(p). In arguing that they were not, Generix relied on the fact that FDA had approved other drug products containing the same active ingredients as its drugs. Such prior FDA approval, Generix argued, was evidence that the active ingredients were generally recognized as safe and effective. From this premise, Generix contended that its products were not "new drugs" even if their inactive ingredients and methods of compounding were not identical to those used in the products previously approved by the FDA.[6] Generix presented no evidence that its drugs had been used to a material extent or for a material time.

The government contended that FDA's prior approval of drugs containing the same active ingredients as the drugs marketed by Generix was irrelevant because the Act requires FDA preclearance of every drug product, unless that product is generally recognized as safe and effective and has been used to a material extent or for a material time. The government's evidence established that Generix's unapproved drug products were not generally recognized by qualified experts as safe and effective (Tr. 49-52, 93-94, 96-97).

In addition, the government presented evidence showing why distribution of unapproved generic drugs poses a danger to the public health. As expert witnesses explained, prescription drugs generally contain

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[5] R. 79-81; see also R. 28 n.3.

[6] R. 106-149, 197-207, 212-224; Tr. 26-27, 250-253.

one or more active ingredients, usually comprising only about 10% of the total compound. They also contain other ingredients, known as excipients, whose purposes are to coat or bind the active ingredients into a convenient form and to control their solubility (Tr. 83-84). Because of differences in these inactive ingredients or in methods of compounding, drugs containing the same active ingredients can differ from each other in the amounts of the active ingredients that enter the bloodstream and the rate at which this occurs.[7] Since the quantity and delivery speed of active ingredients are critical factors that determine the effect of a drug on the patient, it cannot be assumed that a copy of an approved drug will achieve the same therapeutic effect as the pioneer product (Tr. 39-40, 46-47). Often it does not.

The unapproved drugs distributed by Generix include drugs prescribed for the treatment of serious and potentially life-threatening conditions, such as high blood pressure (Tr. 47-48). The government's experts demonstrated that differences in formulation could affect the safety or effectiveness of such drugs (Tr. 94-98). Because the labeling of these generic products is virtually identical to the labeling of the brand name products they copy and because Generix markets these unapproved drugs in a way that leads physicians to believe that they are interchangeable

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[7] The quantity and delivery speed of active ingredients to the bloodstream is referred to as "bioavailability" (Tr. 39-42). Drugs with similar "bioavailability" are considered to be "bioequivalent." Because differences in bioavailability are caused by variations in both active and inactive ingredients, and in methods of manufacture, drugs containing the same active ingredients may not be bioequivalent.

with approved drugs (Tr. 45-47), they may create serious dangers to patients.[8]

Finally, the evidence showed that doctors and pharmacologists generally regard premarketing testing and approval as necessary to insure the safety and effectiveness of drugs. Because of the serious dangers that may be created by differences in bioavailability, physicians would not knowingly prescribe an unapproved generic drug (Tr. 55-57). Their willingness to prescribe generic drugs at all is based on their assumption that generic drugs have received FDA approval.[9]

2. On June 12, 1980, the district court issued an order granting in part and denying in part the government's motion for a preliminary injunction (App. C, *infra*, 18a-31a). Rejecting both the government's and Generix's interpretation of the Act, it held that the government had the burden of showing a potential hazard associated with Generix's drugs.[10] The court then found that the government had presented evidence that differences in bioavailability could affect the safety and effectiveness of drugs containing any

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[8] For example, if the products used to treat high blood pressure do not perform properly, the patient is in grave danger either from recurrence of high blood pressure if absorption of the drug is inadequate, or from toxicity if the drug is overabsorbed (Tr. 47-49).

[9] See *United States* v. *Premo Pharmaceutical Laboratories, Inc.*, 511 F. Supp. 958, 963 (D.N.J. 1981); *Pharmadyne Laboratories, Inc.* v. *Kennedy*, 466 F. Supp. 100, 106 (D.N.J.), aff'd on other grounds, 596 F.2d 568 (3d Cir. 1979).

[10] In so doing, it relied primarily on the district court decision in *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, 475 F. Supp. 52 (S.D.N.Y. 1979), rev'd, 629 F.2d 795 (2d Cir. 1980).

one of six active ingredients or combinations of ingredients [11] and enjoined distribution of those drugs. Because such specific evidence was not presented as to Generix's other unapproved generic drugs,[12] however, the court denied the government's motion for preliminary injunction against distribution of those products (*id.* at 31a).[13] The preliminary injunction was stayed pending Generix's appeal (App. D, *infra*, 32a).[14]

3. The court of appeals reversed that portion of the district court's order granting a preliminary injunction. The court expressly declined to follow the recent decision in *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, 629 F.2d 795 (2d Cir. 1980), in which the Second Circuit held that the Act's "new drug" definition applies to drug products, not only to active ingredients, and that FDA approval of a brand name drug does not exempt other new drugs that contain the same active ingredient from the requirement of premarketing approval. Rather, the Fifth Circuit (now the Eleventh Circuit) concluded that in no event is prior FDA approval required for a drug containing the same active ingredient as a previously approved new drug. Thus, it vacated the preliminary injunc-

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[11] Allopurinol, spironolactone, furosemide, chlorothiazide with reserpine, amitriptyline, and diethylpropion hydrochloride (App. C, *infra*, 20a).

[12] Prochlorperazine maleate and chlorthalidone (App. C, *infra*, 20a).

[13] The government's request for an injunction with respect to the manufacturing practice violations was held in abeyance pursuant to agreement of the parties (Tr. 186-187).

[14] On August 27, 1980, the United States moved for reconsideration of the stay order and of the denial of preliminary injunctive relief with respect to certain of the drugs distributed by respondents. These motions were denied by the district court on October 7, 1980.

tion—even as to those drugs for which there was specific evidence that lack of bioequivalence could be dangerous to patients.

The court of appeals acknowledged that there may be differences in therapeutic effect between a pioneer drug product that has been approved by the FDA, and unapproved generic drugs with the same active ingredient but different inactive ingredients (App. A, *infra*, 3a). It also noted the evidence that these differences "may effect [*sic*] the safety and efficacy of the generic drug product," (*ibid.*). But the court of appeals construed the Act not to protect the public from these dangers. The court concluded: "the term 'new drug' as used in [21 U.S.C.] § 321(p) applies only to the active ingredient of a drug product" (*id.* at 15a). The bases for this conclusion were the court's assumptions that "the drugs listed in the sources described in subsection (A) of [21 U.S.C.] § 321(g)(1) are 'drug substances,' not drug products" and that "[i]f 'new drug' refers to the drug product as opposed to the active ingredient, a drug could never 'muster the requisite scientifically reliable evidence of effectiveness' in order to 'drop out of active regulation by ceasing to be a 'new drug'' " as is contemplated by the Act (*id.* at 5a, 7a).[15]

The court of appeals considered the new drug approval procedures of 21 U.S.C. 355 to be unnecessary in the case of generic drugs because, in the court's view, the Act gave the FDA other means to regulate bioavailability and bioequivalence. The court, in addition, concluded that premarketing review of a generic drug by FDA would be contrary to congressional

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[15] The court also thought that the requirement of Section 502(e) of the Act, 21 U.S.C. 352(e), that drugs be identified by generic name in addition to brand name would be inconsistent with the inclusion of the entire drug product rather than just the active ingredient in the definition of "drug."

intent "to encourage generic-name prescribing and thereby lower prices" (*id.* at 10a).

The court remanded the case to the district court with instructions to dismiss the complaint.

REASONS FOR GRANTING THE PETITION

This case presents an important question concerning the authority and responsibility of the Food and Drug Administration to review the safety and effectiveness of generic drugs *before* those drugs are marketed. The decision below permits the marketing of unapproved drugs which are potentially unsafe or ineffective, and therefore dangerous to the health of the users. This is contrary to the language and legislative history of the Federal Food, Drug, and Cosmetic Act, and is at odds with numerous decisions of this Court giving that statute the broadest coverage possible and construing claimed exemptions narrowly to protect the public health. The judgment in the present case is, moreover, in direct conflict with the recent decision of the Second Circuit in *Premo Pharmaceutical Laboratories, Inc.* v. *United States, supra.* Review by this Court is necessary in order to allow the FDA to fulfill its statutory mandate of ensuring the safety and effectiveness of drugs on a uniform, nationwide basis.

1. The statute expressly defines the term "drug" to include drug products. In holding that "drug" refers only to active ingredients, which constitute only 10% of a drug product, the court of appeals ignored the plain language of 21 U.S.C. 321(g)(1)(B). Even the subsection on which the court relied (21 U.S.C. 321(g)(1)(A)) does not support its conclusion.

a. The statutory definition of the term "drug" has four overlapping parts. It includes (21 U.S.C. 321(g)):

> (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formularly, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C) of this paragraph; but does not include devices or their components, parts, or accessories.

As the Second Circuit held in *Premo*, *supra*, generic drug products are "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." 21 U.S.C. 321(g)(1)(B). Thus, they are "drugs" under at least one of the four subsections of the Act's broad definition. 21 U.S.C. 321(g)(1).

In holding that drug products are not drugs, the court below failed to mention 21 U.S.C. 321(g)(1)(B) or to explain why a generic drug product would not fit within this definition. Instead, the court based its holding on the assumption that active ingredients fall within subsection (A) of 321 (g)(1), but that drug products do not. The court stated that the "record shows that the drugs listed in the sources described in subsection (A) * * * are 'drug substances,' not drug products" (App. A, *infra*, 5a). But there is nothing in the record to support that conclusion. On the contrary, the pharmacopeiae mentioned in

21 U.S.C. 321(g)(1)(A) in fact contain monographs for drugs products as well as active ingredients.[16]

More importantly, however, an article need fall within only one of the subsections of 21 U.S.C. 321(g)(1) in order to be a "drug."[17] Regardless of the coverage of subsection (A), generic drug products are drugs as defined in subsection (B).[18]

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[16] For example, the most recent edition of the combined United States Pharmacopeia-National Formulary has monographs not only for furosemide as an active ingredient but also for "furosemide injection" and "furosemide tablets," see *The Pharmacopeia of the United States of America, Twentieth Revision/The National Formulary, Fifteenth Edition* 344-345 (1980). A monograph may exist both for an "official substance," defined as "an active drug entity or a pharmaceutical ingredient * * *," and for a "dosage form," defined as the "finished * * * preparation or product of one or more official substances formulated for use on or for the patient," *id.* at 2.

[17] No inconsistency is created by the fact that active ingredients themselves are also "drugs." Indeed, 21 U.S.C. 321(g)(1)(D) expressly includes within the "drug" definition "articles intended for use as a component of any article [referred to in the preceding] clauses." The term "component" refers to active as well as inactive ingredients of a drug (cf. 21 U.S.C. 355(b)(2)). Therefore, a reading of 21 U.S.C. 321(g)(1) as a whole shows that the term "drug" must refer to drug products as well as to their active ingredients.

[18] The definition of "drug" in the Food and Drug Act of 1906—the predecessor of the Federal Food, Drug, and Cosmetic Act of 1938—also encompassed both drug substances and drug products. Thus, the 1906 definition of "drug" included, "*all medicines and preparations* recognized in the United States Pharmacopoeia or National Formulary for internal or external use, and *any substance or mixture of substances* intended to be used for the cure, mitigation, or prevention of disease of either man or other animals," ch. 3915, Section 6, 34 Stat. 769 (emphasis added).

This definition was changed to the language contained in 21 U.S.C. 321(g) when Congress enacted the 1938 Act. The

b. Since a generic drug product is a drug, the statutory language also compels the conclusion that a determination of whether a generic drug product is a "new drug" must depend on whether *that product itself* can meet the general recognition standard. The Act defines a "new drug" as "[*a*]*ny drug* * * * the composition of which is such that *such drug* is not generally recognized, among experts * * * as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. 321(p)(1) (emphasis added).

The construction of the term "new drug" to include drug products is necessary to avoid creating an exemption from the new drug approval requirement for drugs that could not be approved by FDA if they were subject to 21 U.S.C. 355. As this Court held in *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 631 (1973):

> [W]e cannot construe § 201(p) [21 U.S.C. 321(p)—the definition of "new drug"] to deprive FDA of jurisdiction over a drug which, if subject to FDA regulation, could not be marketed because it had not passed the "substantial evidence" test. To do so "would be to impute to Congress a purpose to paralyze with one hand what it sought to promote with the other." *Clark* v. *Uebersee Finanz-Korp*, 332 U.S. 480, 489 [(1947)].

If a drug is a new drug, it cannot legally be marketed "unless an approval of an application filed pursuant to [21 U.S.C. 355(b)] is effective with respect

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purpose of that change was to *expand* and not to restrict the definition of the term "drug." See S. Rep. No. 646, 74th Cong., 1st Sess. 1 (1935) ("This expansion of the definition of the term 'drug' and the inclusion of devices are essential if the consumer is to be protected against a multiplicity of abuses not subject to the present law").

to *such drug*." 21 U.S.C. 355(a) (emphasis added).[19] This Court has recognized that an NDA (see note 19, *supra*) is applicable to a specific drug product. *USV Pharmaceutical Corp.* v. *Weinberger*, 412 U.S. 655, 664 (1973). Thus, approval of the pioneer drug, even if that drug has the same active ingredient as the generic drug, is not tantamount to approval of a generic copy which may, because of its different inactive ingredients or different methods of manufacture, have a significantly dissimilar effect on the human body.

The statutory specifications of the contents of new drug applications also show that an NDA applies to a particular drug product—not only to its active ingredients. Thus, 21 U.S.C. 355(b) requires the submission of detailed information about components, methods of manufacturing, and labeling of the new drug.[20] This information will be different for each new drug product, even if it has the same active ingredient as a previously approved product. On the basis of the information included in the application, the FDA must determine whether the applicant has shown that the drug is safe and that there is sub-

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[19] The FDA approves new drug applications (NDAs), which are filed pursuant to 21 U.S.C. 355(b).

[20] 21 U.S.C. 355(b) requires that an NDA contain (emphasis added):

> (1) full reports of investigations which have been made to show whether or not *such drug* is safe for use and whether *such drug* is effective in use; (2) a full list of the articles used as components of *such drug*; (3) a full statement of the composition of *such drug*; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of *such drug*; (5) such samples of *such drug* and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for *such drug*.

stantial evidence[21] that it is effective for its intended uses. If the FDA approves the NDA, the subject drug may then be marketed.[22] On the other hand, if the drug is not shown to be safe, or if substantial evidence of its effectiveness is lacking, the FDA will not approve it.[23]

Because expert general recognition requires at least the evidence that would be required to secure new drug approval, general expert recognition of a drug's safety and effectiveness, therefore, must be based on tests to show safety and effectiveness of the drug in question. *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, *supra*, 412 U.S. at 628-632; *Weinberger* v. *Bentex*

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[21] 21 U.S.C. 355(d) defines "substantial evidence" as:

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

[22] If the manufacturer wishes to make any change in the composition or labeling of the approved new drug, it must first submit a supplement to the NDA. See 21 C.F.R. 314.8. If another manufacturer is licensed to produce the same drug, it too must obtain an NDA. If evidence subsequently shows that an approved new drug is unsafe or ineffective or that the applicant has failed to maintain required records or to correct misleading labeling, the FDA, after opportunity for hearing, may revoke approval of the NDA. 21 U.S.C. 355(e).

[23] If the FDA denies approval, judicial review on the administrative record is available to the applicant. 21 U.S.C. 355(h). See *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, *supra*; *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, *supra*, 629 F.2d at 802.

Pharmaceuticals, Inc., 412 U.S.C. 645, 653 (1973). In addition, the general recognition standard requires that the relevant tests be available in the scientific literature to experts generally (*id.* at 652), and that experts generally agree that the testing shows the drug to be safe and effective (*Hynson, Westcott & Dunning, Inc., supra*, 412 U.S. at 632). Even if a drug satisfies the general recognition criterion, it remains a "new drug"—requiring FDA approval—unless it has been used to a material extent and for a material time under other than experimental conditions. 21 U.S.C. 321(p)(2).

Thus, contrary to the court of appeals' conclusion, no drug product can escape new drug status unless that drug itself is recognized by experts as safe and effective and has been used for a material time. *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, *supra*, 629 F.2d at 804-805. There is nothing in the statutory language to suggest that general recognition of a drug's active ingredient or component would take the product out of the "new drug" category.[24]

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[24] The court of appeals reasoned that if general recognition attached to products rather than active ingredients, no drug product could ever achieve "not new" status and the statutory distinction between a "new drug" and other drugs would be "superfluous." App. A, *infra*, 7a. To the contrary, as this Court clearly contemplated in *Hynson*, a drug product could achieve expert general recognition and pass out of "new drug" status at some point after being marketed for a period of time in accordance with an NDA. 412 U.S. at 631. General recognition of that product does not, as the *Generix* court assumed, require general expert knowledge about the ingredients and manufacturing processes of the product. Rather, it is based on expert knowledge of the testing of the particular product. Compare *Generix*, App. A, *infra*, 7a, with pages 13-14, notes 20 & 21, *supra*.

2. The legislative history of the new drug provisions of the 1938 Act, and of the Act's 1962 amendments, confirms that each drug product that has not itself achieved general recognition among experts must be approved by the FDA before it is marketed.

a. The direct stimulus for Congress' enactment of the premarketing approval requirement was the numerous deaths caused by the drug Elixir Sulfanilamide. That drug was itself an untested combination of a widely used active ingredient and a new inactive ingredient; the *inactive* ingredient was responsible for the deaths caused by the drug.[25] To avoid such tragedies in the future, Congress enacted a system of premarketing approval "to prevent the premature marketing of new drugs not properly tested for safety." H.R. Rep. No. 2139, 75th Cong., 3d Sess. 9 (1938). It would be contrary to the clear congressional intent for courts to eliminate the requirement of premarketing safety review simply because another drug containing the same active ingredient has been proved safe and effective. A statute with such an exemption would not have prevented the Elixir Sulfanilamide tragedy that prompted Congress to mandate premarketing review.

b. The 1962 amendments to the Act were intended to *strengthen* the protection afforded the public by

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[25] See *United States* v. *An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 797-798 (1969); *AMP, Inc.* v. *Gardner*, 389 F.2d 825, 829-830 (2d Cir.), cert. denied, 393 U.S. 825 (1968); S. Doc. No. 124, 75th Cong., 2d Sess. (1937); C. Dunn, *Federal Food, Drug, and Cosmetic Act, A Statement of its Legislative History* 1316-1327 (G.E. Stechert & Co. 1938).

prohibiting the marketing of drugs whose effectiveness has not been established.[26] Thus Congress added to the requirement of testing for safety the further requirement that substantial evidence of effectiveness be demonstrated before the FDA can approve a new drug application. A corresponding change was made in the definition of "new drug" so that henceforth drugs could not escape "new drug" status unless their effectiveness as well as their safety was recognized by qualified experts.

There is nothing in the language or the legislative history of these amendments that suggests Congress meant to weaken the new drug provisions by exempting generic drugs from the premarketing approval requirements of 21 U.S.C. 355. To be sure, as the court of appeals noted, there was a congressional concern with promoting competition in the drug industry. But promoting price competition is not inconsistent with insuring the safety and effectiveness of all products on the market. While Congress sought to encourage competition and the use of less expensive generic drugs,[27] it assumed that no drug would reach the market unless its safety and effectiveness were established through general recognition or an approved NDA. It did not intend to sacrifice safety or effectiveness for lower prices.[28]

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[26] See H.R. Rep. No. 2464, 87th Cong., 2d Sess. 1 (1962); S. Rep. No. 1744, 87th Cong., 2d Sess. 8 (1962).

[27] Much of the discussion in the legislative history of the need to improve competition related to proposals—never enacted—that would have limited terms of drug patents. Proponents of those proposals recognized that, as reported, the [1962] amendment "will have only a very limited effect on prices * * *. Its major result will be to improve the quality of drugs." S. Rep. No. 1744, 87th Cong., 2d Sess. 33 (1962).

[28] The generic name labeling provisions of 21 U.S.C. 352(e) cited by the court do not mean that safety and effectiveness

Indeed, the increased competition and reduction in drug prices that Congress sought to foster through generic labeling would be less likely to occur if generic drugs could be marketed without FDA approval. If generic drugs are not subject to premarketing approval, a physician or pharmacist will have no assurance that generic products would be equally as safe and effective as the brand name drugs for which they purport to be substitutes. Therefore, as the government's experts testified in this case, careful doctors and pharmacists would be deterred from administering generic drugs regardless of the cost savings that might be obtained (Tr. 55-57).[29]

c. The FDA has sought to minimize the burden of filing and obtaining approval of generic drug NDAs to the extent consistent with insuring that unsafe or ineffective prescription drugs do not reach the public. For many generic drugs, FDA has determined that complete safety and effectiveness studies need not be submitted by each manufacturer. Instead, manufacturers of certain generic drugs may

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determinations are to be made on a generic basis. Rather, the purpose of these provisions is to encourage use of generic drugs by assisting doctors and pharmacists in identifying generic equivalents and "ascertain[ing] the qualities and specifications of the product, and the competing products." S. Rep. No. 1744, 87th Cong., 2d Sess. 18 (1962). Thus, labeling a drug with the generic name as well as the trade name would aid physicians in deciding "whether to prescribe by the trade name upon which they have come to rely or to prescribe the so-called generic equivalent by using the official name or by authorizing the pharmacist to select a product bearing the official name" (*ibid.*).

[29] See *Pharmadyne Laboratories, Inc.* v. *Kennedy*, *supra*, 466 F. Supp. at 106.

obtain FDA approval by submitting an abbreviated new drug application ("ANDA"). See 21 C.F.R. 314.1(a) and (f).[30] Under this procedure, the manufacturer may establish that the generic drug is safe and effective by showing that it contains the same active ingredient as an approved new drug, and *also* that the two products have equivalent effects on patients. In effect, therefore, the FDA relies on the body of knowledge developed for the pioneer drug product in evaluating the ANDA. The generic drug is deemed safe and effective and the ANDA is approved if the manufacturer of the generic drug shows that there are no differences between the approved drug and the "me-too" drug that will result in differences in their safety or effectiveness.

3. The court of appeals' decision is contrary to numerous decisions of this Court and is in direct conflict with a recent decision of the United States Court of Appeals for the Second Circuit.

a. This Court has long held that the Act must be interpreted to effectuate its purpose—protection of the public health. *United States* v. *Dotterweich*, 320

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[30] The ANDA process applies to copies of pre-1962 drug products for which the FDA has published a notice known as a Drug Efficacy Study Implementation ("DESI") Notice. Most, but not all, of the unapproved drugs Generix was distributing purported to be generic copies of drugs subject to such notices, and the manufacturer therefore could have sought approval under this simplified procedure.

In addition, the FDA has announced a so-called "paper NDA" policy for post-1962 generic drugs. 45 Fed. Reg. 82052 (1980). Under that policy, applicants may rely on the scientific literature, if it provides adequate data, to establish the safety and effectiveness of the pioneer drug. Safety and effectiveness of a generic drug is then established by such literature *plus* the applicant's showing that its generic drug is bioequivalent to the pioneer. 21 C.F.R. 320.22.

U.S. 277, 280 (1943). For this reason, the Court consistently has given a broad meaning to the term "drug" (*United States* v. *An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 798 (1969)) (emphasis added):

> The historical expansion of the definition of drug, and the creation of a parallel concept of devices, clearly show, we think, that *Congress fully intended that the Act's coverage be as broad as its literal language indicates*—and equally clearly, broader than any strict medical definition might otherwise allow.

Similarly, the Court has narrowly construed the exceptions to the new drug approval requirements. *Hynson, Westcott & Dunning, Inc., supra*, 412 U.S. at 629-631.

The court of appeals, however, did just the opposite—it *narrowed* the *definition* of the term "drug" and *broadened* the general recognition *exemption* from the "new drug" provisions. In so doing, it disregarded the statutory language and legislative history, both of which support the fundamental principle—protecting the public health—that has guided the courts in interpreting the Act.[31]

b. The court of appeals' decision conflicts with the Second Circuit's decision in *Premo Pharmaceutical Laboratories, Inc.* v. *United States, supra*. The court held in *Premo* that the term "drug" as used in 21 U.S.C. 321(p) and 355 refers to drug products and not only to their active ingredients. Therefore, a drug product, even if it contains the same active

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[31] The lower courts also have applied this basic principle in construing the Act. See, *e.g.*, *Upjohn Co.* v. *Finch*, 422 F.2d 944, 947 (6th Cir. 1970); *Carter-Wallace, Inc.* v. *Gardner*, 417 F.2d 1086, 1094-1095 (4th Cir. 1969); *United States* v. *Vitasafe Corp.*, 345 F.2d 864, 870 (3d Cir. 1965).

ingredient as an approved new drug, cannot be marketed without FDA approval unless it meets the "general recognition" standard prescribed by 21 U.S.C. 321(p). The Second Circuit also held that "general recognition" of the safety and effectiveness of a generic drug does not arise from approval of a pioneer drug having the same active ingredient; it requires an expert consensus founded on substantial published evidence as to the generic product's own safety and effectiveness.[32]

Other courts also have espoused the interpretation of the Act adopted by the Second Circuit. For example, in *Pharmadyne Laboratories, Inc.* v. *Kennedy, supra*, the court rejected dicta in an earlier Third Circuit decision, *United States* v. *Articles of Drug . . . Lannett*, 585 F.2d 575 (1978)—which had suggested that some or all generic copies of FDA-approved drugs need not themselves undergo FDA premarketing clearance—and agreed with the FDA that the term "new drug" applies to specific drug products. In two other actions, the FDA has obtained injunctive relief against major manufacturers of unapproved new drugs. *United States* v. *Pharmadyne Laboratories, Inc.*, No. 80-1312 (D.N.J., filed May 8, 1980);[33] *United States* v. *Premo Pharmaceutical*

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[32] The district court decision in that case had rejected the manufacturer's argument that the "new drug" definition applied solely to active ingredients. The district court, however, erred in holding that the government had some burden—not met there—to show that a generic copy presented a hazard before premarketing clearance could be required, *Premo Pharmaceutical Laboratories, Inc.* v. *United States, supra.*

[33] In *Pharmadyne*, the defendant consented to a decree of permanent injunction without contesting the government's claim that such relief was appropriate.

Laboratories, Inc., supra.[34] The fact that there have been several cases dealing with the "new drug" status of generic drugs establishes that the issue is a recurring one that should be resolved by this Court.[35]

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[34] The New Jersey district court's comprehensive opinion in *Premo* was based on a lengthy record. The Director of FDA's Bureau of Drugs, as well as the FDA's top biopharmaceutics expert and a number of distinguished experts in the field, testified to the factual basis for the requested relief. The court made detailed findings and rejected the *Lannett* dicta. It specifically found that drugs having the same active ingredient can differ in safety and effectiveness because of variations in inactive ingredients, 511 F. Supp. at 963-964, 981, because of subtle differences in chemical structure of the active ingredients, *id.* at 963-964, 981-982, and because of differences in manufacturing processes, *id.* at 963-965, 982-984. It found that differences between two drugs having the same active ingredient can lead to severe adverse health consequences, including death, *id.* at 992-993, 996. It concluded, on the basis of the evidence before it, that the adulteration provisions of the Act could not be utilized effectively to protect the public from the dangers posed by the marketing of unapproved generic products, *id.* at 976-977, 988-989. Following this decision, Premo consented to a permanent injunction.

[35] The issue of the status of generic drug products has also been raised in another injunction suit against a manufacturer marketing an unapproved generic drug. *United States* v. *Superpharm Corp.*, No. CV-81-0087 (E.D.N.Y., filed Jan. 9, 1981). The defendants consented to an indefinite extension of a temporary restraining order while the question of the court's authority to order recall of the drugs was litigated.

The issue has, in addition, arisen in cases considering the parallel "new animal drug" provisions. See 21 U.S.C. 321(w). In one case, now on appeal to the Eighth Circuit, the district court concluded that differences in inactive ingredients and in manufacturing processes can affect the safety and effectiveness of a drug. See *United States* v. *Undetermined Quantities*

4. The court of appeals' decision will have serious adverse consequences for the public health.

a. The FDA is now confronted with conflicting court of appeals interpretations of the critical new drug provisions of the Act. The confusion and uncertainty that will result from a generic drug marketing rule that differs from one part of the country to another are obvious: under the decision below, the FDA presumably has no authority for preclearance of generic prescription drugs marketed in the Fifth and Eleventh Circuits, while such procedures are required in the Second Circuit.

Unless the decision below is reversed, the FDA will be unable to prevent the marketing of potentially unsafe and ineffective generic drugs. Once these drugs reach the public, the measures available to remove the drugs from the market *after* they have caused harm simply do not provide the protection Congress intended. See, *e.g.*, *United States* v. *Premo Pharmaceutical Laboratories, Inc.*, *supra*, 511 F. Supp. at 988-989. For example, postmarketing measures would not prevent a dangerous drug such as Elixir Sulfanilamide, which killed numerous persons prior to the enactment of the Act,[36] from reaching the public. Indeed, if the FDA were forced to prove

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. . . *Equidantin Nitrofurantoin Suspension*, [1981] Food Drug Cos. L. Rep. (CCH) ¶ 38,120 (E.D. Mo. May 29, 1981), appeal docketed, No. 81-1793 (8th Cir. July 30, 1981). In another animal drug case, the court concluded that the "new animal drug" provision applies to products rather than to active ingredients, but decided that where the pioneer product has been approved by the FDA any generic copy that contains exactly the same ingredients (including both active and inactive ingredients) does not require FDA premarketing approval, *United States* v. *Articles of Drug . . . OXY 500 Scour Tablets*, [1981] Food Drug Cos. L. Rep. (CCH) ¶ 38,132 (D. Minn. Aug. 6, 1981).

[36] See page 16, *supra*.

that a new drug was unsafe or ineffective—rather than merely to show that it had not been approved—the burden of proving safety and effectiveness placed on the manufacturer by Congress would be reversed, and the removal of unsafe or ineffective products from the market would be delayed.

b. The marketing of unapproved generic drugs will lead to one of two unacceptable outcomes. First, if doctors, pharmacists, and the public are *not* informed of the absence of premarketing review to determine safety and effectiveness, patients who use generic drugs will unknowingly be subjected to the risk that the generic drugs will be unsafe or ineffective. The adverse consequences that may result include the possible death of patients who use such drugs.

On the other hand, if the medical profession and the public do become aware of the risk posed by generic drugs that have not been shown to be bioequivalent to approved pioneer drugs, use of generics will predictably decline. The government could not encourage use of drugs whose safety and effectiveness had not been demonstrated, and indeed might have a duty to warn the public not to permit generic substitutions.

Since current law prohibits any drug to be labeled with a notice that it has or has not been approved by the FDA, 21 U.S.C. 331(*l*), the decision below will have a negative impact on sales of generics which *have* been shown to be safe and effective and have been approved. The only way to be assured that a drug product is safe and effective would be for doctors to specify, and pharmacists to dispense, only the pioneer. Such a result would be contrary to the very congressional policy of increased competition upon which the court of appeals sought to premise its decision. Moreover, it would hamper efforts by the FDA, other federal government agencies, and state

governments to foster the use of safe and effective generic substitutes for more costly products.[37]

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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[37] Generally, drug substitution programs, both in the states and in the federal system, allow a physician to veto substitution. For example, under the federal "maximum allowable cost" regulations implementing the Medicare and Medicaid reimbursement statutes, a physician may, by so stating on his prescription, veto substitution, 45 C.F.R. 19.3(a)(3). Physicians may be expected to veto substitution where they cannot be assured that all generic copies of the products they are prescribing have been approved by FDA. For a discussion of state substitution programs and the effect of the generic "new drug" issue on those programs, see *Pharmadyne Laboratories, Inc.* v. *Kennedy, supra*, 466 F. Supp. at 106.

Appendix

APPENDIX A

UNITED STATES COURT OF APPEALS
FIFTH CIRCUIT
UNIT B

Nos. 80-5652, 80-5856 and 80-5857

UNITED STATES OF AMERICA, PLAINTIFF-APPELLEE

v.

GENERIX DRUG CORPORATION, a corporation, LEWIS MICHAEL ORLOVE, GARY R. DUBIN, and OFELIA PEREZ, Individual, DEFENDANTS-APPELLANTS

Sept. 4, 1981

Appeals from the United States District Court
for the Southern District of Florida

Before MARKEY *, Chief Judge, and HILL and THOMAS A. CLARK, Circuit Judges.

JAMES C. HILL, Circuit Judge:

Before a "new drug" may be introduced into interstate commerce it must be approved by the Food and Drug Administration's "new drug application" (NDA) process. 21 U.S.C. § 355(a). Only drugs that are "new drugs" under 21 U.S.C. § 321(p) require an NDA as a condition of marketing. The NDA process is often expensive and time consuming. In the district court, 498 F.Supp. 288, the plaintiff-

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* Chief Judge of the U.S. Court of Customs and Patent Appeals, sitting by designation.

appellee, the United States, alleged that Generix was distributing "new drugs" without approved new drug applications. The United States sought to enjoin this distribution pursuant to 21 U.S.C. § 332. These appeals arise from an order granting in part and denying in part the United States' motion for a preliminary injunction and denying Generix's motion for rehearing and motion to amend order on preliminary injunction. 28 U.S.C. § 1292(a)(1).

The issue in these appeals is whether the definition of "new drug" in the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 321(p) (West 1972) applies to the entire drug product or whether it applies only to a drug's active ingredients. We hold that the language and intent of Congress limits the definition to a drug's active ingredients. Accordingly, we vacate the preliminary injunction issued by the district court.[1]

I.

Definitions are important in this case. Appellant Generix distributes generic drugs. A generic drug is a copy of the active ingredient of another manufacturer's drug product which as has been shown to be safe and effective.[2] A drug product is composed of

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[1] Our resolution of this case was greatly aided by the excellent briefs and arguments of the parties and the thorough opinion of the district court.

[2] "Safe and effective" is a term of art. *See* 21 U.S.C. § 355(b). A "new drug" must be proved "safe and effective" by substantial evidence.

> The term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it

an active ingredient, or incipient, which represents up to 10% of the product, and excipients, such as binders, coating, and capsules, which account for the remainder. Because manufacturing techniques vary, generic drug products often combine an active ingredient that is generally recognized as safe and effective and excipients that are unique to the individual manufacturer.

The active ingredients of Generix's drug products were not generally in issue in the district court proceedings. Rather, the government's experts testified that the variances in excipients due to different manufacturing processes can directly affect the bioavailability of the active ingredient. Bioavailability is a measure of the time it takes for a given drug product to deliver the active ingredient to the particular organ or area. Additionally, the differences in excipients can affect bioequivalence, a measure based on the comparison of one drug to another. Drug products which are bioequivalent can be used interchangeably for the treatment of the same illness.

Both government experts stressed that the differences in bioavailability and bioequivalence between the product originally prepared using the proved safe and effective "pioneer drug" and the product later produced using the same drug with, perhaps, different binders, coatings, etc. may effect the safety and efficacy of the generic drug product. This is especially true where the drug product involved is a sustained

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could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

Section 505(d), 21 U.S.C. § 355(d).

release drug. Differing rates of solubility due to differences in excipients *may* cause "dumping" of the active ingredient into the bloodstream all at once. In drugs where there is high toxicity, this *may* lead to an overdose.

In essence, the government argues that any difference between excipients renders a drug product a "new drug" within the meaning intended by the statute. According to the government, whether the active ingredient is generally recognized as safe and effective is irrelevant to the discussion. Therefore, the government concludes, Generix's products are "new drugs" due to differing excipients. Generix argues that if the active ingredient is generally recognized as safe and effective, the new drug product is not a "new drug" despite differences in excipients.

After reviewing the statute and the case law the district court settled on the following legal standard:

> . . . [t]he manufacturer of the questioned product is entitled to a declaration that its product is not a "new drug" within the meaning of 21 U.S.C. § 321(p), only if the evidence has shown no reasonable possibility that the differences between the excipients in the recognized and questioned products will make the questioned products less safe and effective than the recognized product.

District Court Opinion at 292, *quoting Premo Pharmaceutical Laboratories, Inc.* v. *United States*, 475 F.Supp. 52, 55 (S.D.N.Y. 1979), *reversed* 629 F.2d 795 (2d Cir. 1980). The district court then concluded that the government's experts had raised a reasonable possibility that the safety and effectiveness of certain Generix drug products were suspect because of their excipients. The court further con-

cluded that Generix had not refuted the government's proof. Accordingly, the district court enjoined Generix from distributing their products which contained allopurinal, spironolactone, furosemide, chlorothiazide with reserpine, amitriptyline, and diethylpropion hydrochloride. District Court Order at 294. The district court refused to enjoin the distribution of Generix products containing prochloreperazine meleate and chlorthalidone. *Id.*

II.

In determining whether or not the term "new drug" refers only to the active ingredient of a drug product, as distinguished from excipients, we turn first to the relevant statutes.

Title 21 U.S.C. § 321(g)(1) defines a "drug" as follows:

> (g)(1) The term 'drug' means (A) articles recognized in the official United States Pharmacopoeia official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure of any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C) of this paragraph; but does not include devices or their components, parts, or accessories.

21 U.S.C. § 321(g)(1). The record shows that the drugs listed in the sources described in subsection (A) of § 321(g)(1) are "drug substances" not drug products.

More importantly, Title 21 U.S.C. § 321(p) defines "new drug" as follows:

> (1) Any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . .; or
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> (2) Any drug . . . the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

21 U.S.C. § 321(p).

Under subsection (2), after a period of time has elapsed and marketing experience has been acquired, a "new drug" substance will no longer be considered a "new drug" requiring an approved NDA to be marketed. As the Supreme Court has noted:

> Under subsection (2) [21 U.S.C. § 321(p)(2), a drug cannot transcend "new drug" status until it has been used "to a material extent or for a material time." Yet, a drug cannot be marketed lawfully before an NDA has been approved by the Commissioner on the basis of "substantial evidence." As the Solicitor General argues, "the Act is designed so that drugs on the market, unless exempt, will have mustered the requisite scientifically reliable evidence of effectiveness long before they are in a position to drop out of active regulation by ceasing to be a 'new drug.'

Weinberger v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 631, 93 S.Ct. 2469, 2484, 37 L.Ed.2d 207 (1973).

If "new drug" refers to the drug product as opposed to the active ingredient, a drug could never "muster the requisite scientifically reliable evidence of effectiveness" in order to "drop out of active regulation by ceasing to be a 'new drug.'" This is so because the factors that bear on the safety and effectiveness of a specific product—manufacturing techniques, quality control, and the precise manner of formulating the finished dosage—are not part of the information made known to the medical community.

Indeed, as we are informed by counsel, a significant part of such information is a closely guarded trade secret that may not be revealed by the F.D.A. *See* 21 U.S.C. § 331(j). Specifically, FDA regulations prohibit public disclosure of certain information in a new drug application, including manufacturing methods and processes, quality control procedures and quantitative and semiquantitative formulas. 21 C.F.R. § 314.14(g). In addition, only the identity of inactive ingredients previously disclosed may be released. *See* 21 C.F.R. § 321(p)(2). Accordingly, the "general recognition" test called for by § 321(p) must apply to a drug product's active ingredient. Otherwise, each new drug product would be considered a "new drug" and § 321(p)(2) would be superfluous.[3]

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[3] In reaching our decision we have carefully considered the opinions of the Third Circuit, *United States* v. *Articles of Drug (Lannett)*, 585 F.2d 575 (3d Cir. 1978) and the Second Circuit, *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, 629 F.2d 795 (2d Cir. 1980.) Our primary reliance,

III.

In effect, the FDA's interpretation of the Act would create a product-by-product licensing system.[4] In ad-

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however, has been on the language and intent of Congress. Although we reach a different result, we agree with the Second Circuit that the FDA "is usually better equipped by reason of its expertise to make the determination" of whether a drug product is safe and effective. 629 F.2d at 804. However, simply because the FDA is better suited to assess the safety and effectiveness of drug products does not mean that Congress authorized the broad grant of jurisdiction that the government argues for in this case.

[4] The government argues that the FDA's interpretation of the Act's new drug provisions is entitled to considerable deference since the FDA is the agency charged with the responsibility of administering the Act. *United States* v. *Rutherford*, 442 U.S. 544, 99 S.Ct. 2470, 61 L.Ed.2d 68 (1979). As a general proposition, of course, this is correct. However, this principle does not mandate that we ignore the plain language and history of the Act. *Espinoza* v. *Farah Mfg. Co.*, 414 U.S. 86, 94-95, 94 S.Ct. 334, 339-340, 38 L.Ed.2d 287 (1973). Furthermore, as Generix points out, the FDA's position on the definition of "new drug" has changed several times since 1938. For example, the FDA exempted drug products from the NDA process by issuing "not new drug" letters until 1968. 40 Fed. Reg. at 26, 143. Even when that policy was discontinued the FDA still maintained an interpretation of "new drug" which supports Generix' position.

> [T]he agency fully realized that it would not be feasible from an administrative standpoint, or necessary for protection of the public health, *or consistent with the definition of new drug in section 201(p) of the act to require either a full or an abbreviated NDA for all human prescription drugs.*

40 Fed. Reg. at 26, 144 (emphasis added).

Around 1968, the FDA commenced the practice of approving what is known as an "abbreviated NDA" or ANDA, to regulate drugs whose safety and effectiveness are well-

dition to rendering the statutory language useless, such an interpretation is plainly contrary to the Congressional intent.[5] Congress did not deal extensively with the role of generic drugs when the Food, Drug and Cosmetic Act was initially enacted in 1938. However, the House Report did state that "this [section 505, U.S.C. § 355] is not a license provision, but is intended merely to prevent the premature marketing of new drugs not properly tested for safety." H.R. Rep. No. 2139, 75th Cong., 3d Sess. 9 (1938).

The 1938 Legislation was amended in 1962 by the "Drug Industry Act of 1962." *See* Senate Rep. No. 1744, 87th Cong , 2d Sess. 1962 U.S. Code Cong. & Ad. News 2884. Generic drugs played a central role in this legislation.

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established. The legal validity of this regulatory hybrid is questionable. *See Hoffmann-La-Roche, Inc.* v. *Weinberger*, 425 F.Supp. 890 (D.C.C. 1975). It is interesting to note the district court's comment that FDA's laxness in enforcing the NDA system stemmed in part from FDA's fear "that it would have a difficult time in court contending that a specific version [of an established drug] is a new drug within the meaning of 21 U.S.C. § 321(p) . . . ." Id. at 892-93.

In sum, the FDA's shifting interpretation of "new drug" provides no basis for affording the FDA interpretation great deference.

[5] We note that there are isolated references which support the government's position. For example, the sponsors of the 1962 Drug Amendments stated:

> every brand new *product*, and every claim for an existing *product*, would be subject to the tests and procedures established in Section 505 of the act [21 U.S.C. 355] 108 Cong. Rec. 17366 (August 23, 1962) (emphasis added).

However, isolated references in the legislative history can not overcome the plain language and override logic of the Act.

The legislation originated as the result of an investigation by the Senate Subcommittee on Antitrust and Monopoly. *See* S.Rep. No. 1744, 87th Cong., 2d Sess., 1962 U.S. Code Cong. & Ad. News 2887. That Subcommittee was concerned with the large profit and tight market control of a few large companies in the drug industry. The Subcommittee found that "one of the principal factors underlying this market control was the success of major drug companies in persuading physicians to prescribe drugs by the companies' trade names despite the existence of less expensive, chemically identical generic-named drugs." Note, *Drug Amendments of 1962-Generic Name Prescribing: Drug Price Panacea*, 16 Stan.L.Rev. 649, 651-52 (1963). Accordingly, the 1962 amendments were designed, in part, to encourage generic-name prescribing and thereby lower prices. *See* Views of Senator Estes Kefauver *et al.*, *reprinted in* 1962 U.S. Code Cong. & Ad. News 2898.

The reasoning of Congress, which we set out in full, follows:

> Most drugs have what is often called a generic name; that is, a nonproprietary name recognized in the official compendia or by common usage. This legislation uses the term "official name," and permits the Secretary to designate the official name in certain circumstances. Section 9 (a) of the bill, as amended, would require that the label of every drug bear the official name with the conspicuousness required by section 502(c) of the Food, Drug, and Cosmetic Act; that is, so as to make it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

Many drugs are marketed under brand names which serve to identify a particular product coming from a particular source. It provides the incentive for the manufacturer to maintain quality surpassing the minimum.

At the same time, the brand name does not sufficiently identify the chemical structure of the drug. The use of the generic or official name is important so that practitioners and pharmacists can turn to the official compendia and other literature to ascertain the qualities and specifications of the product, and the competing products. The committee does not feel that the statute should specify the relative prominence of trade names and official names. It does feel, however, that the statute should specify that the official name be shown with sufficient conspicuousness so that practitioners and pharmacists can easily see it. Thus, competition would be fostered in two ways. The trade name would continue to be prominent, with its assurance of identity of source so that manufacturers could continue to have the incentives to strive for the widest possible distribution and sales. At the same time, to the extent that other manufacturers can market a competing product meeting the same specifications, the conspicuous showing of the official name will lend opportunities for such competition to flourish. The choice will then be left to physicians as to whether to prescribe by the trade name upon which they have come to rely or to prescribe the so-called generic equivalent by using the official name or by authorizing the pharmacist to select a product bearing the official name.

S.Rep. No. 1744, 87th Cong., 2d Sess.; 1962 U.S. Code Cong. and Ad. News 2893-2894.

Excipients are unique to each individual drug manufacturer. Hence, if they are included within the definition of generic drug no drug could ever obtain an "official" or "generic" name through general recognition as is contemplated by the above Congressional language.[6]

---

[6] Generix urges that because the FDA has sought to establish the result they seek in this case through Congressional action and that Congress has declined to so act, we may infer that the government's position in this case is invalid. We reject this argument and agree with the government that the failure of Congress to enact legislation that would clarify or modify an agency's authority in a particular area does not limit the agency's existing power under its current statute. As the Supreme Court has noted, "[p]ublic policy requires that agencies feel free to ask [Congress for] legislation which will terminate or avoid adverse contentions and litigations." *Wong Yang Sung* v. *McGrath*, 339 U.S. 33, 47, 70 S.Ct. 445, 453, 94 L.Ed. 616 (1950). The Court has also noted:

> [t]he advocacy of legislation by an administrative agency—and even the assertion of the need for it to accomplish a desired result is an unusual and unreliable, and not a highly desirable, guide to statutory construction. The possibility of its use to prove more than its means may, but should not, deter administrative agencies from seeking helpful clarification of authority or a fresh and specific Congressional mandate.

American Trucking Ass'n v. *Atchison T. & Santa Fe Ry. Co.*, 387 U.S. 397, 418, 87 S.Ct. 1608, 1619, 18 L.Ed.2d 847 (1967).

Furthermore, we agree with the government that any attempt to rely on proposed legislation would be even more inappropriate in this case because of the number and variety of the bills involved. In the 96th Congress alone there were approximately nine bills (including H.R. 54, 2217, H.R. 4248, S. 772, S. 774, S. 780, S. 1045, S. 1075, S. 1138) that would have amended in different ways, the new drug provisions of the Act.

IV.

In the 1962 Amendments to the Act, Congress provided the means to regulate the excipients in a drug product containing an approved generic drug without subjecting the drug product to the new drug approval process. Specifically, the FDA may invoke the drug provisions of 21 U.S.C. § 351 to insure that a drug is not "adulterated." The FDA may find that a drug is adulterated (1) if there have been inadequate controls in its manufacture, § 351(a); (2) if the strength, quality or purity differ from the official compendium, § 351(b); if the strength of a drug is misrepresented, § 351(c); or if a drug's mixture with another substance reduces "its quality or strength." § 351(d). Presumably the FDA could regulate bioavailability and bioequivalence through the provisions of § 351.

As the Senate Report stated:

> Section 5 of the bill, as amended, is intended to give the Food and Drug Administration additional authority to require that sound methods, facilities, and controls be used in all phases of drug manufacture and distribution. By an amendment of section 501(a)(2) of the Food, Drug, and Cosmetic Act, a drug would be deemed to be "adulterated" if such methods, facilities or controls were found not to conform to current good manufacturing practice to assure safety, identity, strength, quality and purity of the product.
>
> This section, together with the registration and factory inspection provisions of sections 3 and 4

> of this amended bill, would greatly increase the Food and Drug Administration's authority over drug manufacture and distribution. These provisions should prove helpful in reaching persons who are responsible for putting drugs of questionable or unknown quality on the market.

S.Rep. No. 1744, 87th Cong., 2d Sess.; 1962 U.S. Code Cong. & Ad. News 2884, 2890.

V.

The gist of the government's argument is that if drug products are not subject to the NDA process their safety and effectiveness can not be properly regulated as required by 21 U.S.C. § 321(p). It may well be good public policy to regulate the bioavailability and bioequivalence through the NDA or some equivalent process. However, we have found that the statutory language and history of the Food, Drug and Cosmetic Act does not require such approval. The judicial branch may not legislate to fill perceived voids in public policy. Our Constitution leaves that job to Congress. *See Wilson* v. *First Houston Investment Corp.*, 566 F.2d 1235, 1243-45 (5th Cir. 1978) (Hill, J., dissenting) *vacated in light of Transamerica Mortgage Advisors, Inc.* v. *Lewis*, 444 U.S. 11, 100 S.Ct. 242, 62 L.Ed.2d 146 (1979). For example, scientific studies since 1962 might provide a strong argument that excipients should be included in the definition of "new drug." Such a decision necessarily implicates complex chemical and pharmacological considerations. The judicial branch is not equipped properly to assess such considerations.

In sum, we hold that Congress legislated that the term "new drug" as used in § 321(p) applies only to the active ingredient of a drug product. Accordingly, we vacate the preliminary injunction issued by the district court.

VACATED and REMANDED with instructions to DISMISS.

APPENDIX B

UNITED STATES COURT OF APPEALS
FOR THE FIFTH CIRCUIT

October Term, 19

No. 80-5652, 80-5856, 80-5857

D.C. Docket No. 79-6655-CIV-NCR

UNITED STATES OF AMERICA, PLAINTIFF-APPELLEE

versus

GENERIX DRUG CORPORATION, ET AL,
DEFENDANTS-APPELLANTS

Appeal from the United States District Court
for the Southern District of Florida
at Fort Lauderdale

Before MARKEY, Chief Judge *, HILL and THOMAS A. CLARK, Circuit Judges.

JUDGMENT

This cause came on to be heard on the transcript of the record from the United States District Court for the Southern District of Florida, and was argued by counsel;

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* Chief Judge of the U.S. Court of Customs and Patent Appeals, sitting by designation.

ON CONSIDERATION WHEREOF, It is now here ordered and adjudged by this Court that the order of the District Court appealed from, in this cause be, and the same is hereby, vacated; and that this cause be, and the same is hereby remanded to the said District Court with instructions in accordance with the opinion of this Court.

IT IS FURTHER ORDERED that the plaintiff-appellee pay to the defendant-appellants, the costs on appeal to be taxed by the Clerk of this Court.

September 4, 1981

Issued as Mandate:

APPENDIX C

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

Case No. 79-6655-Civ-NCR

UNITED STATES OF AMERICA, PLAINTIFF

vs.

GENERIX DRUG CORPORATION, a corporation, and LEWIS MICHAEL ORLOVE, and GARY R. DUBIN, and OFELIA PEREZ, individuals, DEFENDANTS

ORDER ON MOTION FOR PRELIMINARY INJUNCTION

This matter came before the court on plaintiff's motion for a preliminary injunction pursuant to 21 U.S.C. § 332. Plaintiff has alleged that defendant, Generix Drug Corporation, distributes "new drugs" without an approved new drug application, and that such activity is proscribed by 21 U.S.C. § 355(a). Additionally, plaintiff has alleged that defendants have failed to comply with 21 U.S.C. § 351(a)(2)(B) which requires that repacking and labelling of drugs be performed only in circumstances that comply with current good manufacturing practices. The parties in open court announced that they had reached an amicable agreement with respect to the latter allegation. The parties declined to stipulate the evidence presented could be considered on the issue of a permanent injunction as permitted under Rule 65(a)(2).

The court having heard the testimony of witnesses, having read and considered exhibits received into evidence, having heard the arguments of counsel and

considered the memoranda filed in this matter, hereby enters its findings of fact and conclusions of law.

FINDINGS OF FACT

1. Defendant, Generix Drug Corporation, is a distributor of human drugs with a trade name of "Goldline" and has a plant in Hollywood, Florida.

2. Defendant ships its generic formulations containing the active ingredients listed below in interstate commerce, without approved new drug applications (NDAs):

Allopurinol
Spironolactone with hydrochlorothiazide
Furosemide
Diethylpropion hydrochloride
Chlorothiazide with reserpine
Amitriptyline with perphenazine
Prochloreperazine maleate
Chlorthalidone

3. The above listed active ingredients, with the exception of chlorothiazide with reserpine, are generally recognized among qualified experts as safe and effective and each has been used to a material extent and for a material time for the uses recommended in the labelling employed by defendant.

4. Allpurinol is a drug widely used for the treatment of gout.

5. Spironolactone is a drug used in the treatment of hyper-aldosteronism and in the treatment of a variety of edematous conditions.

6. Furosemide is one of the most widely-used drugs in the United States, and is used to treat hypertension and edema.

7. Diethylpropion hydrochloride is a drug which is used as an adjunct in treating obesity, and is listed in relevant pharmacological text books as an "anorectic".

8. Chlorothiazide with reserpine is a combination of drugs used in the treatment of hypertension. Each drug has been widely used and each is well known, although studies on the specific combination of chlorothiazide with reserpine are not readily available.

9. Amitriptyline with perphenazine is a drug used in the treatment of anxiety and depression.

10. Defendant's "Goldline" formulations containing the following active ingredients have not been tested nor are they generally recognized among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs as safe and effective under the conditions of use prescribed, recommended or suggested in defendant's labelling:

Allopurinol
Spironolactone
Furosemide
Diethylpropion hydrochloride
Chlorothiazide with reserpine
Amitriptyline

11. No evidence relative to the safety and effectiveness of defendant's "Goldline" formulations containing the active ingredients of prochloreperazine maleate or chlorthalidone was presented at the hearing.

CONCLUSIONS OF LAW

The question presented in this cause is a narrow one. It involves interpretation and application of

21 USC § 321(P), which defines the term "new drug" as it is used in the Federal Food, Drug and Cosmetic Act, 21 USC § 301 *et seq.* The statute provides that:

> The term "new drug" means—
>
> > Any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the condition prescribed, recommended, or suggested in the labeling thereof, ...
> >
> > Any drug . . . the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

The introduction or delivery for introduction of "new drugs" into interstate commerce without approval of a new drug application (NDAs) violates 21 USC § 355(a), and such conduct can be enjoined pursuant to 21 USC § 332.

It appears clear that defendants ship "Goldline" products in interstate commerce without having filed new drug applications (NDA). Therefore, the only remaining task is to determine whether these specific generic drug products are "new drugs". Clearly this task is not a simple one; only a few courts have considered the question, and the interpretations of the statute have been rather varied.

After hearing testimony, this court is of the opinion that this difficulty flows from the complex nature of pharmaceutical manufacturing. The government's

first expert, Dr. Roger Palmer, explained the factors and variables involved. Each drug product is composed of an active ingredient, or incipient, which represents up to 10% of the product, and excipients, such as binders, coating, and capsules, which account for the remainder.

A generic drug product represents an attempt by one pharmaceutical manufacturer to copy the drug product of another manufacturer where the active ingredient and excipients in the latter's formulation have been shown to be safe and effective. Because manufacturing techniques and variables differ, each copy of the recognized formulation combines the active ingredient which is generally recognized as safe and effective and excipients unique to the individual manufacturer.

The government's experts testified that the variances in excipients due to different manufacturing processes can directly affect the bioavailability of the active ingredient. Bioavailability is a measure of the time it takes for a given drug product to deliver the active ingredient to the particular organ or area. Additionally, the differences in excipients can affect bioequivalence, a measure based on the comparison of one drug to another. Drug products which are bioequivalent can be used interchangeably for the treatment of the same illness.

Both government experts stressed the differences in bioavailability and bioequivalence between the proved safe and effective "pioneer drug" and the copy may affect the safety and efficacy of the generic drug product. This is especially true where the drug product involved is a sustained release drug. Differing rates of solubility due to differences in excipients may cause "dumping" of the active ingredient

into the bloodstream all at once. In drugs where there is high toxicity, this may lead to an overdose.

In essence, the government argues that any difference between excipients renders a drug product a "new drug" within the meaning intended by the statute; the fact that an active ingredient is generally recognized as safe and effective is irrelevant to the discussion, according to the government. Therefore, it is suggested, "Goldline" products of defendant are "new drugs" due to differing excipients. With equal vigor defendants argue that if the active ingredient is generally recognized as safe and effective, the new drug product is not a "new drug" despite differences in excipients.

APPLICABLE CASE LAW

The judicial trail is not clearly defined. Worse than having a fork in the trail, there are three sets of tracks which go off in three widely divergent directions.

In *United States* v. *Articles of Drug (Lannett)*, 585 F.2d 575 (3d Cir. 1978) *rehearing denied en banc*, the Third Circuit, by way of dictum, flatly rejected the same argument advanced by the government here and accepted Lannett's argument that "all that is required by the 'new drug' section—general safety and effectiveness recognition—has been provided and that bioavailability, bioequivalence and other quality control tests are irrelevant as to safety and efficacy." *Id.* at 582.

After a reading of *Lannett*, it becomes apparent that the Third Circuit did not have before it the type of evidence that has been offered in this cause. The evidence presented to this court is clear: differences in excipients can affect bioavailability and

bioequivalence, and bioavailability and bioequivalence are intimately intertwined with safety and effectiveness.

In *Pharmadyne Laboratories, Inc.* v. *Kennedy*, 466 F. Supp. 100, 102 (DCNJ 1979) a district court within the Third Circuit, commenting on *Lannett*, extensively criticized the Third Circuit's dictum which it perceived as a serious misconstruction of the statutory definition of the term "new drug". In reasoning to the conclusion that the FDA's argument was indeed supported by the statute, the court stated:

> In § 355(b), an NDA is to have a "full list of articles used as components of such drug" and a "full description of the methods used in and the facilities and controls used for, the manufacturing processing and packing of such drug."
>
> Components of a drug may well be (and usually are) things in addition to active ingredients. They may be the binder that permits the active ingredient to be administered in tablet form. Tablets often have an inert coating designed to encase the active ingredients to be administered in tablet form and to permit them to be swallowed. Capsules have an encasement which dissolves in the digestive tract permitting release of the active ingredients. If these inert ingredients were a concern of Congress for a novel drug, it is entirely unclear to me why they would not be of similar concern in the manufacture of a "me-too" product. . . . If the tablet is too hard, or the binder indigestible so that the active ingredients are not released properly or timely, the drug's efficacy may be impaired or destroyed. If the covering of a capsule is not

> readily digestible the same result may occur. *Id.* at 103-104.

Additionally, the court reasoned that when taken as a whole, the statute evinces Congress' concern about individual formulation factors:

> It is argued that Congress made a legislative determination that such factors should be weighed in NDA approval of a novel compound by eschewed them with respect to their latter "me-too" counterparts. While that result may rationally obtain if one looks only at § 321, consideration of the statute as a whole seems to me to lend greater credence to the alternative interpretation advocated by the FDA. Clearly if I were construing the meaning of "new drug" without binding authority, I would opt for the FDA's construction. *Id.* at 104.

The Third Circuit affirmed *Pharmadyne Laboratories* and did not address the district court's dictum on the "new drug" question. *Pharmadyne Laboratories*, 596 F.2d 573 (3rd Cir. 1979).

Premo Pharmaceutical Laboratories Inc. v. *United States*, 475 F. Supp. 52 (S.D.N.Y. 1979) appears to rest on the vast expanse of middle ground between *Lannett* and *Pharmadyne Laboratories*. In *Premo*, the court considered a suit for declaratory relief brought by a manufactuer seeking a declaration that its product was not a "new drug". The manufacturer contended that "insulase", its product, is not a "new drug" because it contains chloropropamide, the active ingredient in "Diabinese", an FDA approved drug manufactured by Pfizer Laboratories. In addressing this issue, the court rejected both the *Lannett* view that no generic drug is a "new drug" if the active

ingredient is generally recognized as safe and effective, and the *Pharmadyne* view that Congress intended that an NDA be filed for each drug product. The court reasoned that:

> In interpreting the term "new drug", the court is mindful that some differences in excipients do affect the safety and effectiveness of a drug product but that others do not, and that Congress has entrusted the FDA, not the court, with finally determining the safety and effectiveness of drugs. Accordingly, when the active ingredient in a questioned drug product is the same as the active ingredient in a drug product already on the market and generally recognized as safe and effective, and when the excipients in the two products are generally recognized individually to be safe, the *manufacturer* of the questioned product *is entitled to a declaration that its product is not a "new drug"* within the meaning of 21 U.S.C. § 321(P), only *if the evidence has shown no reasonable possibility that the differences between the excipients in the recognized and questioned products will make the questioned products less safe and effective than the recognized product. Id.* at 55. (*emphasis added*).

After a careful review of the case law, the statute, and the arguments of the parties, the court is convinced that the rule enunciated in *Premo Pharmaceuticals* is the proper one. It permits the marketing of "me-too" drugs without "costly and time consuming FDA approval," *Premo Pharmaceuticals*, 475 F.Supp. at 55, and prevents the "cumbersome and time consuming case-by-case institution of condemnation actions to rid the market of dangerous 'me-too' drugs." *Id.*

As has been previously mentioned, the action in *Premo* was a suit for declaratory relief filed by the manufacturer. And there "plaintiff introduced credible scientific and medical testimony, amply supported by the scientific literature introduced into evidence, that the differences in the bioavailability of Diabinese and Insulase will not make the latter less safe or effective than the former." *Premo Pharmaceutical* at 56. Because the government only met the plaintiff's proof by showing a theoretical possibility that one product was less safe and effective than the other due to differences in bioavailability, it failed to carry its burden of showing "some reasonable possibility that these differences in the bioavailability of these products will affect the safety or effectiveness of Insulase." *Id.* at 51.

There is no reason why the appropriate rule, as announced in *Premo Pharmaceutical*, cannot be fitted to a case such as the instant one where the FDA has moved for a preliminary injunction. There are two principles which guide the court's hand in fashioning such a rule. First the Federal, Food, Drug & Cosmetic Act is intended primarily to insulate the public from dangerous substances:

> By the Act of 1938, Congress extended the range of its control over illicit and noxous articles and stiffened the penalties for disobedience. The purpose of this legislation thus touches phases of the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self-protection. Regard for these purposes should infuse construction of the legislation if it is to be treated as a working instrument of government and not merely a collection of English words. *United States* v. *Dotterweich*, 320 U.S. 277, 280 (1943).

Second, under 21 U.S.C. § 332, an injunction may issue where it is shown that there has been a violation of the statute:

> There is a sufficient showing where, as here, the government presents evidence of violations of the provisions of a statute enacted for the protection of the public (*citations omitted*). Nor is it necessary to demonstrate the precise way in which violations of the law might result in injury to the public interest. It is sufficient to show only that the threatened act is within the declared prohibition of Congress. (citations omitted). It is sufficient here to show that "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man . . . was and is being distributed in violation of the Food and Drug Act. *United States* v. *Nutrition Service, Inc.*, 227 F. Supp. 375 (N.D. Pa. 1964), *Aff'd.* 347 F.2d 233 (3rd Cir. 1965).

See also United States v. *Medwick Laboratories*, 416 F. Supp. 832 (N.D.Ill. 1976). It is unnecessary, therefore, for the court to consider the four elements generally required to support a motion for preliminary injunction. *See generally Canal Authority* v. *Gallaway*, 489 F.2d 567, 572 (5th Cir. 1974); *Blackshear Residents* v. *Romney*, 472 F.2d 1197 (5th Cir. 1973).

Accordingly, this court holds that the government is entitled to an order enjoining the distribution of generic drugs alleged to be "new drugs" within the meaning of 21 U.S.C. § 321(P), where the government demonstrates that there is some reasonable possibility that differences between the copied drug product and the generic drug product affect the safety and effectiveness of the generic drug product.

In applying the rule as set forth above to the facts as developed at the hearing, the court concludes that the government has carried its burden with respect to certain "Goldline" drug products. Dr. Palmer testified that the "Goldline" drug products used to treat hypertension are not generally recognized a safe and effective, nor are there any known tests of these products. Dr. Barr agreed with Dr. Palmer, and stated that he does not believe that "Goldline" products are safe and effective. Additionally, with regard to specific formulations, Dr. Barr testified that generic versions of drugs containing the active ingredients furosemide and chlorothiazide have formulation problems, and generic formulations containing the active ingredient spironolactone have severe formulation problems. Defendants' formulations of allopurinol and amitriptyline, in Dr. Barr's opinion, are not safe and effective and sustained released drugs, such as defendant's formulation of diethylpropion hydrochloride, pose substantial danger because "dumping" may occur where the formulation is not proper, thus contributing to the possibility of overdose.

The government has shown by the evidence a reasonable possibility that defendants' drugs are not safe and effective. Because the government's experts have raised a reasonable possibility that the safety and effectiveness of defendants' drug products are suspect, it is incumbent upon defendants to produce evidence refuting the government's proof. This defendants have not done. Defendants' expert, Dr. Emil Smith, testified that he would assume that "Goldline" products are equivalent to brand name products, but even he conceded on cross-examination that he would like some assurances that "Goldline" products are similar to brand name products they imitate before the products are marketed.

In reaching its conclusion, the court has not disregarded defendants' arguments that a mere distributor is not the proper party to enjoin and that other distributors or manufacturers have been permitted to continue marketing similar products. These arguments, however, do not prevent the maintenance of this action nor do they persuade the court that the requested relief should not be granted. The statute clearly proscribes the distribution of such drugs into interstate commerce, 21 U.S.C. § 355(a).

Moreover, the court has not ignored evidence of the substantial economic impact caused by a rule requiring generic drug manufacturers or distributors to submit data to the FDA on certain generic drug products. On the contrary, this consideration is embodied in the rule as enunciated; the government has the burden of showing that a particular generic drug product is suspect, and only then is the distributor or manufacturer forced to bear the economic burden of obtaining specific data on its products. An assertion that a generic drug product is not a "new drug" is a shield of sorts, but it is a shield which can be pierced by competent evidence. Likewise the "new drug" definition cannot, in the opinion of this court, be construed so as to permit the wholesale disruption of the generic drug industry merely because the FDA calls a generic drug product a "new drug".

The government has also requested that defendants be ordered to recall the "Goldline" products in question. However, the court cannot conclude on the evidence presented to this point that a recall of the "Goldline" products in issue as requested by the government has been proved necessary.

Accordingly, it is

ORDERED AND ADJUDGED that plaintiff's motion for a preliminary injunction is granted in part and denied in part. It is further

ORDERED AND ADJUDGED that defendants shall cease, until further order of this court, distribution into interstate commerce "Goldline" products containing the following active ingredients:

allopurinol
spironolactone
furosemide
chlorothiazide with reserpine
amitriptyline
diethylpropion hydrochloride.

It is further

ORDERED that the motion for preliminary injunction is denied as to defendants' drug products containing prochloreperazine meleate and chlorthalidone. It is further

ORDERED that plaintiff's request for a recall of the above listed drug products is hereby denied.

DONE AND ORDERED this 12 day of June, 1980.

/s/ *Norman C. Roettger, Jr.*
United States District Judge

APPENDIX D

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

Case No. 79-6655-Civ-NCR

UNITED STATES OF AMERICA

vs.

GENERIX DRUG CORPORATION, ET AL.

THIS CAUSE is before the court on motion of defendant, Generix Drug Corporation, for a stay and for rehearing.

Upon consideration of the record, it is

ORDERED AND ADJUDGED that the motion to stay pending appeal is hereby granted. It is

FURTHER ORDERED that the motion for rehearing is hereby denied.

DONE AND ORDERED this 21 day of August, 1980.

/s/ *Norman C. Roettger, Jr.*
U.S. District Judge

APPENDIX E

21 U.S.C. 321 provides in pertinent part:

For the purposes of this chapter—

* * * * *

(g) (1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formularly, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C) of this paragraph; but does not include devices or their components, parts, or accessories.

* * * * *

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a

new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to June 25, 1938, it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

* * * * *

21 U.S.C. 355 provides:

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) of this section is effective with respect to such drug.

(b) Filing application; contents

Any persor may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug.

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

Within one hundred and eighty days after the filing of an application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) of this section applies, or

(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) of this section on the question whether such application is approv-

able. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he

has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

(e) Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw

approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) that the application contains any untrue statement of a material fact: *Provided*, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application

shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (j) of this section or to comply with the notice requirements of section 360(j)(2) of this title, or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based.

(f) Revocation of order refusing, withdrawing or suspending approval of application

Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) of this section refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Service of orders

Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the Department designated by the Secretary or (2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) Appeal from order

An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals or the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order

complained of was entered, as provided in section 2112 of title 28. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28. The commencement of proceedings under this subsection

shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

(i) Exemptions of drugs for research; discretionary and mandatory conditions; direct reports to Secretary

The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon—

(1) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

(2) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings; and

(3) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b) of this section.

Such regulations shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where they deem it not feasible or, in their professional judgment, contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs.

(j) Records and reports; required information; regulations and orders; access to records

(1) In the case of any drug for which an approval of an application filed pursuant to this

section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section: *Provided, however,* That regulations and orders issued under this subsection and under subsection (i) of this section shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

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Joint Appendix

Supreme Court, U.S.
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APR 15 1982
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CLERK

No. 81-1222

In the Supreme Court of the United States

OCTOBER TERM, 1981

UNITED STATES OF AMERICA,

Petitioner

v.

GENERIX DRUG CORPORATION, ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE ELEVENTH CIRCUIT

JOINT APPENDIX

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PETITION FOR WRIT OF CERTIORARI FILED DECEMBER 30, 1981
CERTIORARI GRANTED MARCH 1, 1982

In the Supreme Court of the United States

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JOINT APPENDIX

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DISTRICT COURT DOCKET ENTRIES

DATE		PROCEEDINGS
1979		
Nov.	29	COMPLAINT.
	29	Motion for Preliminary Injunction
	29	Memo in support of motion for preliminary injunction (w/Exhibits attach.)
	29	Affidavit of Adam J. Trujillo, Director, Orlando District Atlantic Field Office of the U.S. Food & Drug Administration, in support of motion for preliminary injunction.
	29	Summons issued as to Authorized Representative Generix Drug Corporation. Copy to file.
	29	Summons issued as to defts' Lewis Michael Orlove, Gary Dubin; Ofelia Perez, C/O Generix Drug Corporation. Copy to file.
Dec.	3	Notice of hearing on motion for preliminary injunction, on 12/18/79 @ 9:30 A.M. @ U.S. Courthouse, Ft. Lauderdale, Fla., before Judge Roettger. (Pltf.)
Dec.	13	Joint Motion and Stipulation for Continuance of Hearing date from 12/18/79 to 1/16/1980. (Parties)
Dec.	21	Motion for extension of time to file reply memo. (Defts')
	21	Certificate of service on motion for extension of time. (Defts')
	21	Notice of appearance of Paul J. Levine, Esq. as counsel for Defts.
	26	ANSWER. (Defts)

DATE		PROCEEDINGS
1980		
Jan.	14	Supplemental affidavits in support of Gov't memo in support of motion for preliminary injunction. (Pltf)
Jan.	11	Opposition to Govt's motion for preliminary injunction. (DEFTS)
	11	Memo in support of above pleading. (Defts)
Dec.	14	Summons retd. exec. 12/6/79 as to Gary R. Dubin.
	14	Summons retd. exec. 12/6/79 as to Ofelia Perez.
	14	Summons retd. exec. 12/6/79 as to Authorized Representative Generix Corporation, by serving Kenneth I. Sawyer, Vice Pres.
	14	Summons retd. exec. 12/6/79 as to Lewis Michael Orlove.
Jan.	3	ORDER: Joint motion for continuance of hearing 12/18/79 GRANTED; Hearing reset 1/16/80 @ (9:30) a.m. (NCR)
	24	Supplemental memo in support of Defts' opposition to motion for preliminary injunction. (Deft)
Feb.	1	Reply to Defts' supplemental memo in opposition to motion for preliminary injunction. (Govt)
Jan.	18	ORDER: Deft's motion for extension of time to file reply GRANTED; Deft. shall have thru 1/11/80 to file response to Govt's motion for preliminary injunction. (1/18/80 NCR nunc pro tunc)
Mar.	26	Supplemental memorandum in support of its motion for preliminary injunction. (Gov't)
Apr.	30	Motion for Oral Argument on Motion to Enjoin (Defts.) (Proposed Order att.)

DATE		PROCEEDINGS
1980		
	30	Motion to Enjoin Illegal and Abusive Conduct by Agents of the Food and Drug Administration and the Florida State Department of Health and Rehabilitative Services. (Defts.)
	30	Memo. in Support of above Motion. (Defts.)
	30	Affidavit of Lewis Michael Orlove, Pres. Generix Drug Corp. (Defts.)
May	5	Supplemental Memorandum in Support of Motion to Enjoin Illegal and Abusive Conduct. (Deft. Generix)
	5	Affidavit of Kenneth I. Sawyer.
	5	Affidavit of Norman E. Rubin.
	6	Motion for Extension of Time to File Reply Memorandum. (Pltf.) (Proposed Order att.)
	6	Certificate of Service of above motion. (Pltf.)
	9	Motion to Strike Affidavits (Pltf.) (Proposed Order att.)
	9	Memo. in Support of above motion (Pltf.)
	9	Certificate of Service on above pleadings (Pltf.)
	12	Supplemental Memorandum in Opposition to Government's Motion for Preliminary Injunction (Defts.)
March	24	Notice to take depositions on 4/15/80 of the following: JOHN MARCHELEWICZ & LeGRAND C. BURNS, M.D. @ 8:30 a.m. in Montpelier, Vermont. (Pltf.)
May	22	Deposition of Legrand C. Burns, M.D. taken 4/15/80 @ 9:30 a.m. in Montpelier, Vermont.
	27	Deposition of John Marchelewicz taken 4/15/80 @ 8:30 a.m. in Montpelier, Vermont.

DATE		PROCEEDINGS
1980		
	19	Letter from Thomas Scarlett, Esq. to Joseph I. Bogart RE: Copy of attachment to Deft's. Supplemental Memo. in Opposition to Gov't Motion for Preliminary Injunction att. (Deft. Generix)
	27	Withdrawal of Motion to Enjoin Illegal and Abusive Conduct by Agents of the Food and Drug Administration and the Florida State Department of Health and Rehabilitative Services. (Defts.)
	30	Government's Memo. in Reply to Deft's. Supplemental Memo. of May 12, 1980. (Pltf.)
June	13	ORDER: Pltf's. Motion for preliminary injunction is GRANTED IN PART and DENIED IN PART. Defts. shall cease, until further order of this court, distribution into interstate commerce "Goldline" products containing the following active ingredients: Allopurinol; spironolactone; furosemide; chlorothiazide w/reserpine; amitriptyline; and diethylpropion hydrochloride. Motion for preliminary injunction DENIED as to defts'. drug products containing prochloreperazine maleate and chlorthalidone. Pltf's. request for a recall of the listed drug products is DENIED. (6/12/80 NCR)
	13	ORDER: Sua Sponte court reserves the right to make corrections as to form in order on motion for preliminary injunction entered 6/12/80. (NCR)
June	23	Notice of appearance of the law firm of Greene & Cooper, P.A. as additional counsel for Defts.
	23	Motion for Rehearing and Motion to Amend Order on Motion for Preliminary Injunction, w/Memo of Law. (Defts.)

DATE		PROCEEDINGS
1980		
	23	Motion to Stay Preliminary Injunction Pending Appeal and to Expedite Final Hearing. (Defts.)
	23	Affidavit of Lewis Michael Orlove, President of Generix Drug Corp.
July	7	Interrogatories propounded by Defts. to Pltf.
	7	Motion to Shorten Time to Answer Interrogatories (Defts.)
	9	Reply to Government's Response to Defts'. Motion and Memo of Law. (Defts.)
May	8	ORDER: Deft. Generix's motion to enjoin illegal and abusive conduct by Pltf. and Fla. State Dept. of HRS set for hearing 5/12/80 @ 10 a.m., before Judge Roettger, U.S. District Court, Ft. Lauderdale, Fla. (5/7/80 NCR)
July	21	Certificate of service of interrogatories propounded by Pltf. to Defts.
Aug.	11	Letter from Gerald C. Kell, Atty., to Clerk W/Pltf's Answers to Defts' Interrogatories Attached.
	11	*NOTICE OF APPEAL* filed by Defts. from Order on motion for Preliminary Injunction entered 6/12/80. (Copies to USCA; U.S. Atty; Eagle, Esq.; Asst. Chief Counsel for Drugs,: Kell, Esq. and Burditt & Calkins)
	21	Transcript of proceedings held 1/15/80. Pages 1 thru 257.
	21	ORDER: Deft's motion to stay pending appeal GRANTED; Deft's motion for rehearing DENIED. (NCR)
Aug.	19	Motion to Compel Answers to Interrogatories Propounded to Pltf. by Defts. W/Memorandum of Law.
	18	Answers to First set of Interrogatories. (DEfts)
	26	CLERK'S CERTIFICATE.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

No. ———

UNITED STATES OF AMERICA, PLAINTIFF

vs.

GENERIX DRUG CORPORATION, a corporation, and LEWIS MICHAEL ORLOVE, and GARY R. DUBIN, and OFELIA PEREZ, individuals, DEFENDANTS

COMPLAINT FOR INJUNCTION

The United States of America, plaintiff, by J.V. Eskenazi, United States Attorney for the Southern District of Florida, respectfully represents to this Honorable Court as follows:

1. This proceeding is brought under Section 302(a) of the Federal Food, Drug, and Cosmetic Act (21 United States Code 322(a)), which section specifically invests the United States District Courts with jurisdiction to enjoin and restrain violations of said Act.

2. Defendant Generix Drug Corporation is a corporation organized and existing under the laws of the State of Florida, and is trading and doing business at 3050 North 28th Terrace, Hollywood, Florida, within the jurisdiction of this Court.

3. Defendant Lewis Michael Orlove is the president of said corporation, and is the most responsible individual of the corporation. He represented management in discussions with Food and Drug Administration (FDA) investigators, stating that he intended to see that current good manufacturing practice (CGMP) deviations were corrected. He instructed defendants Dubin and Perez not to sign or comment on affidavits. Defendant Orlove performs his duties as outlined above at 3050 North 28th Terrace, Hollywood, Florida, within the jurisdiction of this Court.

4. Defendant Gary R. Dubin is a vice-president of said corporation and reports directly to Defendant Orlove. His responsibilities include the ordering of drug products for the firm and handling complaints received pertaining to all of the drug products distributed by the corporation. Defendant Dubin has sent letters to customers and sales personnel of Generix Drug Corporation, relating the Generix philosophy and position regarding sales of new drug products. He represented management in discussions with FDA investigators and has corresponded with FDA personnel regarding recalls, distribution and CGMP deviations. Defendant Dubin performs his duties as outlined above at 3050 North 28th Terrace, Hollywood, Florida, within the jurisdiction of this Court.

5. Defendant Ofelia Perez is responsible for the repacking operations of the corporation, liaison with all government agencies, and the security of controlled drug substances handled by the corporation. Defendant Perez reports directly to Defendant Dubin. Defendant Perez performs her duties as outlined above at 3050 North 28th Terrace, Hollywood, Florida, within the jurisdiction of this Court.

6. The defendants are now and/or have been engaged at their plant at 3050 North 28th Terrace, Hollywood, Florida, in distributing in interstate commerce drugs which are "new drugs", within the meaning of 21 United States Code 321(p); for which no approvals of applications filed pursuant to 21 United States Code 355(b) are in effect and no notices of claimed investigational exemption that comply with 21 United States Code 355(i) and 21 CFR 312.1 are on file for such drugs.

7. The defendants have been and are now also engaged at their plant at 3050 North 28th Terrace, Hollywood, Florida, in packing, labeling, and storing various articles of drug within the meaning of 21 United States Code 321(g) (including but not limited to those articles identified in paragraph 6 of this Complaint), holding for sale said articles of drug after shipment in interstate

commerce and distributing said articles of drug in interstate commerce.

8. The aforesaid articles of drug which are packaged and labeled by the defendants are adulterated within the meaning of 21 United States Code 351(a)(2)(B) in that the methods used in, and the facilities and controls used for, their packing, labeling, and holding do not conform to and are not operated and administered in conformity with current good manufacturing practice, as set forth in 21 CFR 211, to assure that such drugs meet the requirements of said Act as to safety and have the identity and strength, and meet the quality and purity characteristics, which they purport and are represented to possess.

9. Defendants violate 21 United States Code 331(d) by introducing and causing to be introduced and delivering for introduction and causing to be delivered for introduction into interstate commerce, in violation of 21 United States Code 355(a), those articles of drug set forth in paragraph 6.

10. Defendants violate 21 United States Code 331(a) by introducing and causing to be introduced, and delivering for introduction and causing to be delivered for introduction into interstate commerce, articles of drug which are adulterated as set forth in paragraph 8.

11. Defendants violate 21 United States Code 331(k) by their acts of packing and labeling articles of drug, which acts are done while the articles are held for sale after shipment in interstate commerce and result in the articles being adulterated as set forth in paragraph 8.

12. The most recent FDA inspection, conducted on June 11-15, 1979, was made to determine if the defendants had corrected the deviations from current good manufacturing practice revealed during a March 20-April 11, 1979 inspection of defendants' facilities (see paragraph 13, below). Defendants had made written and oral representations to FDA officials at a meeting on

May 29, 1979, that corrections either had been or were being made. This inspection disclosed that, while some corrections had been made, significant and continuing deviations from CGMP's (as set out in 21 CFR 211) still exist, including, but not limited to, the following:

(a) Master production and control records are inadequate (21 CFR 211.186) in that:

(1) There was no written procedure describing the preparation of the master production and control records—records were signed as approved by a variety of individuals with no indication that these individuals were designated by the firm to perform these functions;

(2) Not one of the master records was signed and dated by a second person to reflect that the information had been independently checked as complete and accurate;

(3) One of twelve products repacked since the previous inspection was repackaged without a master production record and another of the twelve products was repackaged using a master production record that did not reflect any approval signatures;

(b) Appropriate laboratory controls had not been established to assure that incoming bulk drug products conform to appropriate standards of identity (21 CFR 211.160(b)) in that:

(1) There were no written specifications with which to compare the incoming product;

(2) Although the firm's standard operating procedure states that retention samples from previous lots will be used as standards, two products were noted for which no retention

samples were present and which were released for repackaging without comparison with retention samples;

(c) Distribution records reflecting lot or control numbers were not maintained for any repackaged drug product (21 CFR 211.196);

(d) No quality control unit had been established and there were no written procedures governing the responsibilities and procedures applicable to all of the various quality control unit functions (21 CFR 211.22);

(e) There was no available stability data on file for at least six repackaged drug products (21 CFR 211.166).

13. A more comprehensive FDA inspection of the defendants' plant conducted on March 20 through April 11, 1979, disclosed significant deviations from current good manufacturing practice as set forth in 21 CFR 211, including, but not limited to, the following:

(a) There were no master production and control records for any repacked drug products (21 CFR 211.186);

(b) Appropriate laboratory controls had not been established to assure that incoming bulk drug products conform to appropriate standards of identity (21 CFR 211.160(b));

(c) Distribution records reflecting lot or control numbers were not maintained for any repackaged drug (21 CFR 211.196);

(d) No quality control unit had been established and there were no written procedures governing the responsibilities and procedures applicable to all of the various quality control unit functions (21 CFR 211.22);

(e) There was no available stability data on file for drug products that were being repackaged (21 CFR 211.166);

(f) Labeling records were inadequate in that labeling records have, in some cases, been prepared or altered after the completion of the labeling operations (21 CFR 211.188);

(g) Drug product production and control records were not, in at least two instances, adequately reviewed prior to the release and distribution of the lots; these two instances resulted in products being labeled with incorrect lot numbers (21 CFR 211.192).

14. Inspections conducted by the Food and Drug Administration on July 10-12, 14, 18, 1978 and July 22, 25-29, 1977, at the defendants' plant disclosed equally significant and, in some cases, identical deviations from current good manufacturing practice as those found in March through April 1979. These deviations include the lack of master production and control records, lack of stability data for repacked drugs, lack of adequate control over labeling operations, failure to adequately review and approve all records prior to release of a batch, and failure to record lot numbers on distribution records.

15. The defendants are well aware that their activities are in violation of the law as show by the following:

(a) Defendants have had numerous warnings regarding the marketing of new drugs without approved applications:

(1) On November 21, 1978, at the request of FDA's Orlando District, an official of the Florida Department of Health and Rehabilitative Services issued a "Notice to Remove from Sale" all lots and sizes of the drug, furo-

semide tablets (40 mg.) and the drug diethylpropion hydrochloride tablets (75 mg.). These drug products were manufactured by Pharmadyne Laboratories, Hackensack, New Jersey, and distributed by the defendants. The notice was received and signed for by Defendant Perez. The reason for withdrawal states: "Lack of Approved NDA." These products were subsequently seized by a Deputy United States Marshal on December 26, 1978 (78-6539-CIV-JE).

(2) A "Dear Customer" letter, dated November 13, 1978, signed by Defendant Dubin and distributed by the firm, discussed the fact that defendants are distributing drugs without approved NDA's (new drug applications) or ANDA's (abbreviated new drug applications) and erroneously assures customers that FDA guarantees "a high degree of drug safety, strength, purity and effectiveness . . ."

(3) On December 12, 1978, another "Notice to Remove From Sale" was issued to the defendants by the Florida Department of Health and Rehabilitative Services at the request of FDA's Orlando District for all lots and sizes of the drugs, furosemide tablets and chlorothiazide with reserpine tablets. (Generix labeling of the latter tablets refers to chlorothiazide by the name "Diurigen".) The "Reason for Withdrawal" states: "At request of FDA. No NDA; Lack of stability data." These articles were subsequently seized on April 11, 1979 (79-6181-CIV-NCR).

(4) On January 10, 1979, the Deputy United States Marshal for the Southern District of Florida seized the article of drug, spironolactone with hydrochlorothiazide tablets, in the

possession of the defendants. The seizure was based on new drug charges (79-6006-CIV-JE).

(5) On January 18, 1979, a "Notice to Remove from Sale" covering all lots and sizes of amitriptyline hydrochloride and perphenazine tablets was issued to the defendants by the Florida Department of Health and Rehabilitative Services and signed for by Defendant Perez. The reason for withdrawal again stated: "Requested by FDA . . . No NDA." These articles were subsequently seized on April 11, 1979 (79-6144-CIV-JLK).

(6) A letter dated January 26, 1979, signed by Defendant Dubin and distributed to the corporation's sales personnel, discusses the drugs furosemide and chlorpropamide and the NDA question. The letter contains the statement "the new products are still subject to seizure *at our level and manufacturers*, thus the recommendation that your customers stock up" (emphasis in original).

(7) On February 26, 1979, a "Notice to Remove from Sale" was issued to the defendants by the Florida Department of Health and Rehabilitative Services again at the request of FDA and signed for by Defendant Perez, covering lots of furosemide tablets and diethylpropion hydrochloride tablets received by the defendants subsequent to the previous seizure of these drugs on December 26, 1978. These drugs were seized on April 11, 1979 on new drug charges (79-6181-CIV-NCR).

(8) On March 21, 1979, another "Notice to Remove from Sale" was issued to the defendants by the Florida Department of Rehabilitative

Services, covering all lots and sizes of the following drugs: allopurinol tablets (100 mg. and 300 mg.), diurigen with reserpine tablets (250 mg. and 500 mg.), furosemide tablets (20 mg. and 40 mg.), spironolactone plus tablets, prochlorperazine maleate capsules and diethylpropion hydrochloide tablets. The reason for withdrawal was again at FDA's request, because there was no NDA in effect for these products. On April 4, 1979, a second "Notice to Remove from Sale" covering amitriptyline plus and diethylpropion hydrochloride was issued at National Airlines Freight Terminal, Fort Lauderdale, Florida. These were drugs that the defendants returned to the manufacturer after they were observed by FDA investigators. The manufacturer refused redelivery and returned the drug products to Florida. The drugs were subsequently returned to the defendants, still under the "Notice to Remove from Sale". All these drugs were seized on September 18, 1979 (79-385 -CIV-SMA).

(9) On May 29, 1979, FDA Orlando District officials stated at a meeting with the firm that distribution of New Drugs without an approved New Drug Application was in violation of the Federal Food, Drug, and Cosmetic Act. Defendants Dubin and Perez were present at the meeting, and Defendant Orlove was represented by the firm's General Counsel and Vice-President. The firm, through its General Counsel, stated that it was not presently and would not in the future market drugs that are in violation of the law. Further inspection on June 11-15, 1979, disclosed the continuing distribution of unapproved new drugs. Among these were drugs which were

the subject of previous "Notice to Remove from Sale" and seizures.

(10) On September 19, 1979, the FDA Orlando District Office received a brochure entitled "Goldline's BIG DEAL by Generix Drug Corp." The brochure featured at least five drugs which have been identified through publication in the *Federal Register* as new drugs requiring approved new drug applications. One of the drugs, Spironolactone Plus Tablets, was the subject of a prior seizure.

(11) On October 22, 1979, FDA issued Notices of Detention and Hearing for two shipments of a drug, Chlorthalidone 50 mg. Tablets. The articles were also manufactured in Canada and imported by the defendants. The articles were detained on a charge of being new drugs without an approved new drug application.

(b) Defendants have had numerous warnings regarding failure to operate in accordance with current good manufacturing practice:

(1) Inspection of the firm in July 1977, revealed deviations from current good manufacturing practice. The deviations were discussed with Defendant Perez at the close of the inspection and a written list of inspectional observations was given to her.

(2) On October 13, 1977, an Information Letter was sent to Defendant Orlove, outlining the GMP deviations found during the July 1977 inspection. No response was received.

(3) The firm was again inspected in July 1978. Deviations of essentially the same nature and severity were found. These were again pointed out to Defendants Orlove and Perez, verbally

and in writing at the conclusion of the inspection.

(4) On December 12, 1978, a "Notice of Adverse Findings" was sent to Defendant Orlove, outlining the GMP deviations found during the July 1978 inspection. Defendant Orlove responded on January 10, 1979, promising correction.

(5) The firm was inspected in March through April 1979 to see whether the corrections had been made. Identical and continuing deviations of a serious nature still existed, as summarized hereinbefore in paragraph 13. A list of observations was left with Defendant Orlove after it was discussed with him and Defendants Dubin and Perez.

(6) As a result of errors involving incorrect lot numbers found by FDA investigators during the March/April, 1979 inspection, the firm recalled two drug products: spironolactone tablets, 25 mg. and d.o.s. (dioctyl sodium sulfosuccinate) capsules, 100 mg.

(7) On May 29, 1979, at a metting with FDA Orlando District officials, Defendants Dubin and Perez and Kenneth Sawyer, Vice-President and General Counsel for Generix Drug Corporation, representing Defendant Orlove, made both written and oral representations that all deviations from current good manufacturing practice had been or were being corrected.

(8) The firm was re-inspected on June 11-15, 1979, to determine if the corrections referred to in sub-paragraph (7) had been accomplished. Although some corrections had been made, continuing deviations of a serious na-

ture still existed, as summarized hereinbefore in paragraph 12. Another list of observations was issued to Mr. Orlove and discussed with him and defendants Dubin and Perez.

16. Despite the aforesaid written and oral warnings including seizure of many products and their announced intention to comply with the Act, the defendants continue to distribute new drugs within the meaning of 21 United States Code 321(p), contrary to the provisions of 21 United States Code 355(a), and to pack, label, hold and distribute articles of drug which are adulterated, as hereinbefore alleged.

17. Plaintiff is informed and believes that unless restrained by this Honorable Court the defendants will continue to violate 21 United States Code 331(d) and plaintiff further believes that unless restrained by this Honorable Court, defendants will continue to violate 21 United States Code 331(a) and (k), in the manner hereinbefore alleged.

WHEREFORE PLAINTIFF PRAYS:

1. That the defendants, Generix Drug Corporation, Inc., a corporation, and Lewis Michael Orlove, Gary R. Dubin, and Ofelia Perez, individuals, and all of their officers, agents, servants, employees, and attorneys and any and all persons in active concert or participation with them or any of them be perpetually restrained and enjoined under the provisions of 21 United States Code 332 (a) from directly or indirectly doing or causing to be done any of the following acts:

A. Introducing or delivering for introduction into interstate commerce any article of drug for which defendants shall have received notice by letter, *Federal Register* announcement or any other action by the Food and Drug Administration that such drug is a new drug within the meaning of 21 United States Code 321(p), unless and until an approved application filed pursuant to 21 United

States Code 355(b) is effective with respect to said drug, or unless and until an acceptable notice of claimed investigational exemption filed pursuant to 21 United States Code 355 (i) and 21 CFR 312.1 is on file for such drug;

B. Introducing or delivering for introduction into interstate commerce any article of drug which is packed, repacked or labeled at said defendants' plant at 3050 North 28th Terrace, Hollywood, Florida; and packing, repacking or labeling at said plant any article of drug, after shipment of one or more of its components in interstate commerce, unless and until:

I. Methods, facilities and controls for packing, labeling, and holding any article of drug at said plant are established and operated and administered in conformity with current good manufacturing practice as required by 21 CFR 211, which methods, facilities, and controls shall specifically include, but not be limited to, the following:

(a) Establishing adequate Master Production and Control Records for each repacked drug product and written procedures that will ensure, in addition to all other pertinent requirements set forth in 21 CFR 211.186, that:

(i) An adequate Master Production and Control Record for each repacked drug product will be developed, and checked and approved independently by two individuals, prior to repackaging;

(ii) Master Production and Control Records will adequately specify, among other things, the product container, closure, and packaging materials to be used that are consistent with the container/closure system in which stability studies were conducted.

(b) Establishing adequate control procedures, including written specifications and procedures, to verify the identity of incoming bulk dosage form drug products prior to release for repackaging;

(c) Preparing adequate distribution records that contain the lot or control number of each repacked drug product in such a manner that the distribution of each lot can be readily determined to facilitate its recall if necessary;

(d) Establishing a quality control unit and adequate written procedures governing its responsibilities and procedures;

(e) Establishing adequate procedures to assure stability of drug products in their marketed container/closure system;

(f) Preparing complete and accurate labeling control records at the time the operations involved are performed;

(g) Establishing adequate production and control procedures that provide for adequate review and approval by the quality control unit of all production and control records prior to release of a batch and a written record of the investigation of any unexplained discrepancy.

II.

(a) The defendants report, in writing, to the Orlando District Office of the Food and Drug Administration each of the steps they have taken to assure that the methods used in, and the facilities and controls used for, the packing, labeling, and holding of drug products are operated and administered in conformity with the current good manufacturing practice regulations;

(b) Duly authorized Food and Drug Administration representatives are granted free access to defendants' plant for the purpose of making inspections of the plant, including the building, pertinent equipment, finished and unfinished materials, containers, labeling, and all records relating to the

methods used in, and the facilities and controls used for the manufacture, processing, packing and holding of such drugs, as the Food and Drug Administration deems necessary in order to determine that the requirements set forth hereinbefore in subparagraph B, Part I have been met, the cost of any such inspection to be borne by the defendants at the rate of $26.75 per hour and fraction thereof per representative for inspectional work; $32.00 per hour and fraction thereof per representative for laboratory and analytical work; $.17 per mile for travel expense, and $43.00 per representative per day for subsistence expenses, where necessary;

(c) The Orlando District Office of the Food and Drug Administration notifies the defendants in writing that the defendants appear to be in compliance with the requirements set forth hereinbefore in subparagraph B, Part I.

III.

(a) All of the drugs which have been or are in the process of being packed or labeled at defendants' plant, including all bulk drugs for repacking and labeling that are on hand and in the possession of the defendants are examined by the defendants or a person, selected by the defendants, who by reason of training and experience is qualified to make such examinations, under the supervision of and in accordance with methods approved by, the Food and Drug Administration which examination shall include, but not be limited to the following:

(i) A comprehensive review of production and control records for adequacy and completeness;

(ii) A review of test results, reports of analyses, packing, labeling and distribution records to assure that each drug is not adulterated.

(b) After such examinations are concluded reports of these examinations are made by the defendants to the Food and Drug Administration as it deems necessary in order to assure that the articles have the safety, identity, strength, quality, and purity which they purport and are represented to possess.

C. Introducing or delivering for introduction into interstate commerce any article of drug which is packed, repacked, or labeled at said defendants' plant at 3050 North 28th Terrace, Hollywood, Florida; and packing, repacking, or labeling at said plant any article of drug, after shipment of one or more of its components in interstate commerce, after compliance has been made with the provisions of Parts I, II and III of subparagraph B hereinbefore set forth, which is adulterated within the meaning of 21 United States Code 351(a)(2)(B) in that the methods used in, or the facilities or controls used for its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice, as prescribed by regulations 21 CFR 210.3 and 211.1 through 211.208 to assure that such drug meets the requirements of the Federal Food, Drug, and Cosmetic Act as to safety and has the identity and strength and meets the quality and purity characteristics, which it purports or is represented to possess.

2. That the defendants, Generix Drug Corporation, Inc., a corporation, and Lewis Michael Orlove, Gary R. Dubin, and Ofelia Perez, individuals, and all of their officers, agents, servants, employees, and attorneys and any and all persons in active concert or participation with them or any of them be ordered under the provisions of 21 United States Code 332(a) to:

A. Institute recalls, as the Food and Drug Administration deems necessary, of finished drugs distributed by the defendants, which have been identified to the defendants by the Food and Drug Administration by letter, *Federal*

Register announcement, or other action as new drugs for which there are no approved applications or acceptable notices of claimed investigational exemption on file with the Food and Drug Administration, when distributed; and of finished drugs distributed by the defendants which are adulterated or misbranded;

B. Destroy or otherwise bring into compliance with the law all recalled drugs under the supervision of the Food and Drug Administration, and pay all expenses for such supervision at the rates hereinbefore specified.

3. That the defendants and each and all of their officers, agents, servants, employees, and attorneys and any and all persons in active concert or participation with them or any of them be enjoined and restrained as herein prayed during the pendency of this action, that the plaintiff be granted judgment for its costs herein, and that the Court grant such other and further relief as the Court deems just and proper.

J. V. ESKENAZI
United States Attorney

By:
Assistant United States Attorney

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

Case No. 79-6655-Civ-NCR

UNITED STATES OF AMERICA, PLAINTIFF

vs.

GENERIX DRUG CORPORATION, a corporation, and LEWIS MICHAEL ORLOVE, and GARY R. DUBIN, and OFELIA PEREZ, individuals, DEFENDANTS

ANSWER

Defendants, GENERIX DRUG CORPORATION, LEWIS MICHAEL ORLOVE, GARY R. DUBIN, and OFELIA PEREZ, through their undersigned counsel, file this Answer to the Complaint filed herein, and say:

1. Defendants admit the allegations of paragraph 1 of the complaint.

2. Defendants admit the allegations of paragraph 2 of the complaint, except that the name of the corporate defendant is Generix Drug Corp.

3. Defendants admit the allegations of the first, second, and fourth sentences of paragraph 3 of the complaint. Defendants deny the allegations of the third sentence of paragraph 3, except that defendants admit that Kenneth I. Sawyer as General Counsel to Generix Drug Corp. advised officials and employees of Generix that they were under no legal obligation to sign affidavits presented to them by FDA and that defendants Dubin and Perez did not sign such affidavits.

4. Defendants admit the allegations of paragraph 4 of the complaint, except that defendants deny that defendant Dubin's duties include the handling of complaints about Generix's products.

5. Defendants admit the allegations of paragraph 5 of the complaint, except that defendants deny that defendant Perez reports directly to defendant Dubin.

6. Defendants deny the allegations of paragraph 6 of the complaint.

7. Defendants admit the allegations of paragraph 7 of the complaint, except that defendants deny that their activities involve drugs identified in paragraph 6, and deny that the activities described in paragraph 7 take place at the address given.

8. Defendants deny the allegations of paragraph 8 of the complaint.

9. Defendants deny the allegations of paragraph 9 of the complaint.

10. Defendants deny the allegations of paragraph 10 of the complaint.

11. Defendants deny the allegations of paragraph 11 of the complaint.

12. Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations in the first sentence of paragraph 12 of the complaint, except that defendants admit that an inspection occurred during the period specified. Defendants deny the allegations in the second sentence of paragraph 12, except that defendants admit that representatives of Generix Drug Corp. met with FDA officials on May 29, 1979, and stated their intention to make revisions in the operating procedures of Generix. With respect to the remainder of the allegations in paragraph 12, defendants deny that there exist in the operations of the Generix Drug Corp. any deviations from current good manufacturing practices. Defendants deny that any such deviations observed in the past were significant. Defendants affirmatively allege that since the last FDA inspection identified in the complaint, Generix Drug Corp. has refined the procedures employed in its manufacturing activities and that those procedures meet applicable standards of the industry for the activities in question.

13. Defendants deny that significant deviations from CGMPs existed at the time of the inspection identified in paragraph 13 of the complaint. Defendants admit that an inspection occurred during the period specified.

14. Defendants deny that significant deviations from CGMPs existed at the time of the inspections identified in paragraph 14 of the complaint. Defendants admit that inspections occurred during the periods specified.

15. Defendants deny that their activities are in violation of the law, as alleged in the first sentence of paragraph 15 of the complaint. With respect to the allegations in subparagraph (a) of paragraph 15, defendants admit that the administrative and legal actions described therein occurred, but deny that those actions related to new drugs. With respect to the allegations in subparagraph (b) of paragraph 15, defendants admit that the events described therein occurred, but deny that there existed in Generix Drug Corp.'s operations any significant deviations from CGMPs.

16. Defendants deny the allegations of paragraph 16 of the complaint.

17. Defendants are without knowledge and information sufficient to form a belief as to the truth of the allegations in paragraph 17 of the complaint, except that defendants deny that they do now, or will in the future, violate the law.

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS
Attorneys for Defendants
One Biscayne Tower, 3190
2 S. Biscayne Boulevard
Miami, Florida 33131
(305) 371-2200

By: /s/ Paul J. Levine

THOMAS SCARLETT
Morgan, Lewis & Bockius
1800 M. Street, N.W.
Washington, D.C. 20036
Telephone: (202) 872-5096

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that a true and correct copy of the foregoing Answer was mailed to ANA BARNETT, Assistant United States Attorney, 300 Ainsley Building, 14 N.E. 1st Avenue, Miami, Florida 33132, MS. JACQUELINE H. EAGLE, Assistant Chief Counsel for Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20857, and MR. GERALD KELL, Attorney, Consumer Affairs Section, Department of Justice, Washington, D.C. 20580 this 26th day of December, 1979.

/s/ Paul J. Levine
PAUL J. LEVINE

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

No. ———

UNITED STATES OF AMERICA, PLAINTIFF

vs.

GENERIX DRUG CORPORATION, a corporation, and LEWIS MICHAEL ORLOVE, and GARY R. DUBIN, and OFELIA PEREZ, individuals, DEFENDANTS

NOTICE OF MOTION FOR PRELIMINARY INJUNCTION

Please take notice that, upon the complaint in the above entitled action, and the affidavits of Adam J. Trujillo, District Director of the FDA Orlando District Office, and of Jerome A. Halperin, Deputy Director of the FDA's Bureau of Drugs, attached thereto, a motion will be made in this Court at 9:30 on the 18th day of December, 1979, at the opening of the Court on that day or as soon thereafter as Counsel can be heard, for a preliminary injunction against the defendants herein in accordance with the prayer of said complaint and for such other or further relief in the premises as to the Court may seem just and proper.

J. V. ESKENAZI
United States Attorney

By: ———————————
Assistant U.S. Attorney

Attorney for Plaintiff

300 Ainsley Building
14 N.E. First Avenue
Miami, Florida 33132
(305) 350-5472

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

No. ———

UNITED STATES OF AMERICA, PLAINTIFF

vs.

GENERIX DRUG CORPORATION, a corporation, and LEWIS MICHAEL ORLOVE, and GARY R. DUBIN, and OFELIA PEREZ, individuals, DEFENDANTS

MOTION FOR PRELIMINARY INJUNCTION

1. The United States of America, plaintiff herein, moves this Court to grant a preliminary injunction against the defendants, Generix Drug Corporation, a corporation, and Lewis Michael Orlove, Gary R. Dubin, and Ofelia Perez, individuals, and each and all of their officers, agents, servants, employees, and attorneys and those persons in active concert or participation with them, pending final determination of this action, and until the further order of this Court enjoining and restraining them from directly or indirectly doing or causing to be done any of the following acts with respect to articles of drug:

A. Introducing or delivering for introduction into interstate commerce any article of drug for which defendants shall have received notice by letter, *Federal Register* announcement or any other action by the Food and Drug Administration that such drug is a new drug within the meaning of 21 United States Code 321(p), unless and until an approved application filed pursuant to 21 United States Code 355(b) is effective with respect to said drug, or unless and until an acceptable notice of claimed investigational exemption filed pursuant to 21 United States Code 355(i) and 21 CFR 312.1 is on file for such drug;

B. Introducing or delivering for introduction into interstate commerce any article of drug which is packed, repacked or labeled at said defendants' plant at 3050 North 28th Terrace, Hollywood, Florida; and packing, repacking or labeling at said plant any article of drug, after shipment of one or more of its components in interstate commerce, unless and until:

I. Methods, facilities and controls for packing, labeling, and holding any article of drug at said plant are established and operated and administered in conformity with current good manufacturing practice as required by 21 CFR 211, which methods, facilities, and controls shall specifically include, but not be limited to, the following:

(a) Establishing adequate Master Production and Control Records for each repacked drug product and written procedures that will ensure, in addition to all other pertinent requirements set forth in 21 CFR 211.186, that:

(i) An adequate Master Production and Control Record for each repackaged drug product will be developed, and checked and approved independently by two individuals, prior to repackaging;

(ii) Master Production and Control Records will adequately specify, among other things, the product container, closure, and packaging materials to be used that are consistent with the container/closure system in which stability studies were conducted.

(b) Establishing adequate control procedures, including written specifications and procedures, to verify the identity of incoming bulk dosage form drug products prior to release for repackaging;

(c) Preparing adequate distribution records that contain the lot or control number of each repacked

drug product in such a manner that the distribution of each lot can be readily determined to facilitate its recall if necessary;

(d) Establishing a quality control unit and adequate written procedures governing its responsibilities and procedures;

(e) Establishing adequate procedures to assure stability of drug products in their marketed container/closure system;

(f) Preparing complete and accurate labeling control records at the time the operations involved are performed;

(g) Establishing adequate production and control procedures that provide for adequate review and approval by the quality control unit of all production and control records prior to release of a batch and a written record of the investigation of any unexplained discrepancy.

II.

(a) The defendants report, in writing, to the Orlando District Office of the Food and Drug Administration each of the steps they have taken to assure that the methods used in, and the facilities and controls used for, the packing, labeling, and holding of drug products are operated and administered in conformity with the current good manufacturing practice regulations;

(b) Duly authorized Food and Drug Administration representatives are granted free access to defendants' plant for the purpose of making inspections of the plant, including the building, pertinent equipment, finished and unfinished materials, containers, labeling, and all records relating to the methods used in, and the facilities and controls used for the manufacture, processing, packing

and holding of such drugs, as the Food and Drug Administration deems necessary in order to determine that the requirements set forth hereinbefore in subparagraph B, Part I have been met, the cost of any such inspection to be borne by the defendants at the rate of $26.75 per hour and fraction thereof per representative for inspectional work; $32.00 per hour and fraction thereof per representative for laboratory and analytical work; $.17 per mile for travel expense, and $43.00 per representative per day for subsistence expenses, where necessary;

(c) The Orlando District Office of the Food and Drug Administration notifies the defendants in writing that the defendants appear to be in compliance with the requirements set forth hereinbefore in subparagraph B, Part I.

III.

(a) All of the drugs which have been or are in the process of being packed or labeled at defendants' plant, including all bulk drugs for repacking and labeling that are on hand and in the possession of the defendants are examined by the defendants or a person, selected by the defendants, who by reason of training and experience is qualified to make such examinations, under the supervision of and in accordance with methods approved by, the Food and Drug Administration which examination shall include, but not be limited to the following:

(i) A comprehensive review of production and control records for adequacy and completeness;

(ii) A review of test results, reports of analyses, packing, labeling and distribution records to assure that each drug is not adulterated.

(b) After such examinations are concluded reports of these examinations are made by the defendants to the Food and Drug Administration as it deems necessary in order to assure that the articles have the safety, identity, strength, quality, and purity which they purport and are represented to possess.

C. Introducing or delivering for introduction into interstate commerce any article of drug which is packed, repacked, or labeled at said defendants' plant at 3050 North 28th Terrace, Hollywood, Florida; and packing, repacking, or labeling at said plant any article of drug, after shipment of one or more of its components in interstate commerce, after compliance has been made with the provisions of Parts I, II and III of subparagraph B hereinbefore set forth, which is adulterated within the meaning of 21 United States Code 351(a)(2)(B) in that the methods used in, or the facilities or controls used for its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice, as prescribed by regulations 21 CFR 210.3 and 211.1 through 211.208 to assure that such drug meets the requirements of the Federal Food, Drug, and Cosmetic Act as to safety and has the identity and strength and meets the quality and purity characteristics, which it purports or is represented to possess.

2. That the defendants, Generix Drug Corporation, Inc., a corporation, and Lewis Michael Orlove, Gary R. Dubin, and Ofelia Perez, individuals, and all of their officers, agents, servants, employees, and attorneys and any and all persons in active concert or participation with them or any of them be ordered under the provisions of 21 United States Code 332(a) to:

A. Institute recalls, as the Food and Drug Administration deems necessary, of finished drugs distributed by the defendants, which have been identified to the defendants by the Food and Drug Administration by letter, *Federal Register* announcement, or other action as new

drugs for which there are no approved applications or acceptable notices of claimed investigational exemption on file with the Food and Drug Administration, when distributed; and of finished drugs distributed by the defendants which are adulterated or misbranded;

B. Destroy or otherwise bring into compliance with the law all recalled drugs under the supervision of the Food and Drug Administration, and pay all expenses for such supervision at the rates hereinbefore specified, on the grounds that, unless restrained by this Court, the said defendants will continue the violations referred to, as more fully appears from the affidavits of Adam J. Trujillo, District Director, Orlando District of the Food and Drug Administration, and Jerome A. Halperin, Deputy Director, FDA Bureau of Drugs, attached to the Complaint and incorporated by reference here.

Dated: 11/29/79

J. V. ESKENAZI
United States Attorney

By: /s/ Ana Barnett
Assistant U.S. Attorney
Attorney for Plaintiff

300 Ainsley Building
14 N.E. First Avenue
Miami, Florida 33132
(305) 350-5472

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

No. ———

UNITED STATES OF AMERICA, PLAINTIFF

vs.

GENERIX DRUG CORPORATION, a corporation, and LEWIS MICHAEL ORLOVE, and GARY R. DUBIN, and OFELIA PEREZ, individuals, DEFENDANTS

AFFIDAVIT OF ADAM J. TRUJILLO

ADAM J. TRUJILLO being duly sworn, deposes and says:

1. I am Director, Orlando District, Atlanta Field Office of the United States Food and Drug Administration (FDA). My duties as District Director include responsibility for directing, controlling, and supervising the day-to-day operations of the District relating to the enforcement of the Federal Food, Drug, and Cosmetic Act ("the Act").

2. As District Director, I manage field personnel involved in the investigation of Generix Drug Corporation, and have custody and control of official Food and Drug Administration records pertaining to that investigation.

3. In the course of my official duties, I have reviewed our official files concerning Generix Drug Corporation, including, among other things: inspectional reports; sample collection reports; seizure actions; recalls; memoranda of meetings and telephone conversations; and letters to and from defendants. These official records establish the facts in this affidavit.

4. Defendant Generix Drug Corporation is a corporation organized and existing under the laws of the State of Florida, and is trading and doing business at 3050 North 28th Terrace, Hollywood, Florida, within the jurisdiction of this Court.

5. Defendant Lewis Michael Orlove is the president of said corporation, and is the most responsible individual of the corporation. He represented management in discussions with FDA investigators, stating that he intended to see that current good manufacturing practice (CGMP) deviations were corrected. He instructed defendants Dubin and Perez not to sign or comment on affidavits. Defendant Orlove performs his duties as outlined above at 3050 North 28th Terrace, Hollywood, Florida, within the jurisdiction of this Court.

6. Defendant Gary R. Dubin is a vice president of said corporation and reports directly to Defendant Orlove. His responsibilities include the ordering of drug products for the firm and handling complaints received pertaining to all of the drug products distributed by the corporation. Defendant Dubin has sent letters to customers and sales personnel of Generix Drug Corporation, relating the Generix philosophy and position regarding sales of new drug products. He represented management in discussions with FDA investigators and has corresponded with FDA personnel regarding recalls, distribution, and CGMP deviations. Defendant Dubin performs his duties as outlined above at 3050 North 28th Terrace, Hollywood, Florida, within the jurisdiction of this Court.

7. Defendant Ofelia Perez is responsible for the repacking operations of the corporation, liaison with all government agencies, and the security of controlled drug substances handled by the corporation. Defendant Perez reports directly to Defendant Dubin. Defendant Perez performs her duties as outlined above at 3050 North 28th Terrace, Hollywood, Florida, within the jurisdiction of this Court.

8. The defendants are now and/or have been engaged at said plant in distributing in interstate commerce drugs which are "new drugs", within the meaning of 21 United States Code 321(p), for which no approvals of applications filed pursuant to 21 United States Code 355(b) are in effect and no notices of claimed investigational

exemption that comply with 21 United States Code 355(i) and regulation 21 CFR 312.1 are on file for such drugs.

9. The defendants have been and are now also engaged at their plant at 3050 North 28th Terrace, Hollywood, Florida, in packing, labeling and storing various articles of drug within the meaning of 21 United States Code 321(g)(1) (including but not limited to those articles identified in paragraph 6 of the Complaint), holding for sale said articles of drug after shipment in interstate commerce, and distributing said articles of drug in interstate commerce.

10. The following chronology relates to "new drugs" that defendants have shipped in interstate commerce in violation of the New Drug provisions of the Act:

(a) On November 21, 1978, at the request of Orlando District, an official of the Florida Department of Health and Rehabilitative Services issued a "Notice to Remove from Sale" all lots and sizes of the drug, furosemide tablets (40 mg.) and the drug diethylpropion hydrochloride tablets (75 mg.) (Exhibit 1.) These drug products were manufactured by Pharmadyne Laboratories, Hackensack, New Jersey, and distributed by the defendants. The notice was received and signed for by Defendant Perez. The reason for withdrawal states: "Lack of Approved NDA." These products were subsequently seized by a Deputy United States Marshal on December 26, 1978 (78-6539-CIV-JE).

(b) A "Dear Customer" letter, dated November 13, 1978, signed by Defendant Dubin and distributed by the firm, discusses the fact that defendants are distributing drugs without approved NDA's (new drug applications) or ANDA's (abbreviated new drug applications) and erroneously assures customers that FDA guarantees "a high degree of drug safety, strength, purity and effectiveness . . ." (Exhibit 2).

(c) On December 12, 1978, another "Notice to Remove from Sale" was issued to the defendants by the Florida Department of Health and Rehabilitative Services at the

request of FDA for all lots and sizes of the drugs, furosemide tablets and chlorothiazide with reserpine tablets. (Generix labeling of the latter tablets refers to chlorothiazide by the name "Diurigen"). The "Reason for Withdrawal" states: "At request of FDA. No NDA; Lack of stability data." (Exhibit 3). These articles were subsequently seized on April 11, 1979 (79-6181-CIV-NCR).

(d) On January 10, 1979, the Deputy United States Marshal for the Southern District of Florida seized the article of drug, spironolactone with hydrochlorothiazide tablets, in the possession of the defendants. The seizure was based on new drug charges (79-6006-CIV-JE).

(e) On January 18, 1979, a "Notice to Remove from Sale" covering all lots and sizes of amitriptyline hydrochloride and perphenazine tablets was issued to the defendants by the Florida Department of Health and Rehabilitation Services and signed for by Defendant Perez. The reason for withdrawal again stated: "Requested by FDA . . . No NDA" (Exhibit 4). These articles were subsequently seized on April 11, 1979 (79-6144-CIV-JLK).

(f) A letter dated January 26, 1979, signed by Defendant Dubin and distributed to the corporation's sales personnel discusses the drugs furosemide and chlorpropamide and the NDA question. The letter contains the statement "the new products are still subject to seizure *at our level and manufacturers*, thus the recommendation that your customers stock up" (emphasis in original) (Exhibit 5).

(g) On February 26, 1979, a "Notice to Remove from Sale" was issued to the defendants by the Florida Department of Health and Rehabilitative Services at the request of FDA, and signed for by Defendant Perez covering lots of furosemide tablets and diethylpropion hydrochloride tablets received by the defendants subsequent to the seizure of these drugs on December 26, 1978 (Exhibit 6). These drugs were seized on April 11, 1979 on new drug charges (79-6181-CIV-NCR).

(h) On March 21, 1979, another "Notice to Remove from Sale" was issued to the defendants by the Florida Department of Health and Rehabilitative Services covering all lots and sizes of the following drugs: allopurinol tablets (100 and 300 mg.), diurigen with reserpine tablets (250 mg. and 500 mg.), furosemide tablets (20 mg. and 40 mg.), spironolactone plus tablets, prochlorperazine maleate capsules, and diethylpropion hydrochloride tablets. The reason for withdrawal was again at FDA request because there was no NDA in effect for these products (Exhibit 7). On April 4, 1979, a second "Notice to Remove from Sale" covering amitriptyline plus and diethylpropion hydrochloride was issued by the Florida Department of Health and Rehabilitative Services at National Airlines Freight Terminal, Fort Lauderdale, Florida. These were drugs that the defendants attempted to return to the manufacturer after they were observed by FDA investigators. The manufacturer refused redelivery and returned the drug products to Florida. The drugs were subsequently returned to the defendant, still under the "Notice to Remove from Sale" (Exhibit 8). All these drugs are presently awaiting seizure.

(i) On May 29, 1979, I and other FDA employees met with representatives of the firm at their request. At the meeting the firm's representatives, including defendants Dubin and Perez, were informed that distribution of new drugs without an approved new drug application was in violation of the Federal, Food, Drug, and Cosmetic Act. Mr. Kenneth Sawyer, Vice President and General Counsel of the firm and representing defendant Orlove, stated that the firm was not presently and would not in the future market drugs that are in violation of the law.

(j) On June 11-15, 1979, the firm was inspected to determine, among other things, if the firm was in fact marketing drugs in violation of the law. The inspection disclosed that distribution of unapproved new drugs, including drugs that were the subject of previous Notices of Removal from Sale and Seizures, was continuing. Such shipments have been documented by FDA investigators.

(k) On September 19, 1979, the FDA Orlando District Office received a brochure entitled "Goldline's BIG DEAL by Generix Drug Corp." (Exhibit 17). The brochure featured at least five drugs which have been identified through publication in the *Federal Register* as new drugs requiring approved new drug applications. One of the drugs, Spironolactone Plus Tablets, was the subject of a prior seizure.

(l) On October 22, 1979, FDA issued Notices of Detention and Hearing for two shipments of a drug, Chlorthalidone 50 mg. tablets (Exhibit 18). The articles were also manufactured in Canada and imported by the defendants. The articles were detained on a charge of being new drugs without an approved new drug application.

11. In addition to violating the new drug provisions of the Act, defendants adulterate a number of drugs while they are held for sale after shipment in interstate commerce. The adulteration results from packing, labeling, and holding drugs contrary to current good manufacturing practice as set forth in 21 CFR 211.

12. The most recent inspection of defendants' drug manufacturing plant on June 11-15, 1979, disclosed significant deviations from current good manufacturing practice as specifically set forth on the FDA Investigator's List of Observations (a document that was provided to defendants at the completion of the inspection). (See Exhibit 9 attached to this Affidavit.) The inspection disclosed deviations that were the same as those noted during previous FDA inspections.

13. The defendants have been made well aware that their methods and controls used in manufacturing drugs are not in compliance with current good manufacturing practice, as shown by the following:

(a) Inspection of the firm in July 1977, revealed deviations from current good manufacturing practice. The deviations were discussed with Defendant Perez at the close of the inspection and a written List of Inspectional Observations was given to her (Exhibit 10).

(b) On October 13, 1977, an Information Letter was sent to Defendant Orlove, outlining the CGMP deviations found during the July 1977 inspection. No response was received (Exhibit 11).

(c) The firm was again inspected in July 1978. Deviations of essentially the same nature and severity were found. These were again pointed out to Defendants Orlove and Perez, verbally and in writing at the conclusion of the inspection (Exhibit 12).

(d) On December 12, 1978, a "Notice of Adverse Findings" was sent to defendant Orlove, outlining the CGMP deviations found during the July 1978 inspection (Exhibit 13). Defendant Orlove responded on January 10, 1979, promising correction (Exhibit 14).

(e) The firm was inspected in March-April 1979, to see whether the corrections had been made. Identical and continuing deviations of a serious nature still existed, and a List of Observations was again left with the firm (Exhibit 15).

(f) At the May 29, 1979, meeting, referred to in paragraph 10(i), a writen response to the list of observations referred to in paragraph 13(e) was presented (Exhibit 16). The response listed corrections allegedly made or being made. These alleged corrections were discussed during the meeting.

(g) On June 11-15, 1979, the firm was again inspected. Although some corrections had been made, continuing deviations of a serious nature still existed. A List of Observations was again left with the firm (Exhibit 9).

14. Mr. Orlove stated, at the close of the most recent FDA inspection of Generix, that he would discontinue manufacturing drug products on June 18, 1979, until he was convinced that the firm was in compliance with CGMP requirements. In a June 21, 1979 phone call, he informed FDA Inspector Clarence Danielson that the firm was now in compliance with CGMP's. In that conversation, Mr. Orlove stated, however, that he had not yet been able to find a quality control person to assist the

firm to assure complete compliance with CGMP's. In a June 13, 1979 memorandum to a member of his staff, Mr. Dubin stated that any of six unapproved drugs (but not including the drug chlorpropamide) that were returned to Generix by customers should not be placed in inventory but rather should be returned to the manufacturers of those drugs. As discussed above, defendants have, in the past, made assurances to the FDA that they would comply with the law's requirements but have not in fact done so. In light of that history, it is my judgement that neither the June 21 telephone conversation nor the June 13 memorandum demonstrate that defendants are now, or will be in the future, in compliance with the Act.

15. The records establish that, despite FDA warnings, defendants intend to continue shipping certain "new drugs" in violation of the Act. We believe that injunction is necessary to prevent further violations of 21 United States Code 331(d). Also, injunction covering the firm's repacking and labeling operations is necessary to assure compliance with current good manufacturing practice and prevent further violations of 21 United States Code 331(a) and (k), in view of defendants' failure to correct deficiencies identified to them. Statements by defendants that these violations "will be" corrected cannot be taken as evidence of compliance.

16. I hereby verify under penalty of perjury that the foregoing statement is true and correct.

ADAM J. TRUJILLO
Director, Orlando District
Atlanta Field Office, Region IV
Food and Drug Administration

AFFIDAVIT

JEROME A. HALPERIN, being first duly sworn, deposes and says:

1. I am Deputy Director, Bureau of Drugs, United States Food and Drug Administration.

2. In this capacity I am familiar with the Agency's position with respect to the "new drug" status of drug products.

3. Also, in my capacity as Deputy Director I have custody of the Bureau records including New Drug Applications (NDAs) and Notices of Claimed Investigational Exemption for a New Drug (INDs) relating to human drugs on file with the United States Food and Drug Administration.

4. The Federal Food, Drug, and Cosmetic Act prohibits the introduction into interstate commerce of any new drug unless an approval of a new drug application (NDA) filed pursuant to 21 U.S.C. 355(b) is effective with respect to the drug; except that 21 U.S.C. 355(i) permits, subject to regulations, the introduction or delivery for introduction into interstate commerce of unapproved new drugs intended solely for investigational use by experts qualified by scientific training an experience to investigate the safety and effectiveness of drugs (IND).

5. It is the position of the Food and Drug Administration that drug products containing the following active ingredients are new drugs as defined by Section 201(p) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(p):

(a) Allopurinol
(b) Furosemide
(c) Chlorothiazide with reserpine
(d) Spironolactone with hydrochlorothiazide
(e) Diethylpropion hydrochloride
(f) Prochlorperazine maleate
(g) Chlorthalidone
(h) Amitriptyline with perphenazine

6. A diligent search of the official records of the United States Food and Drug Administration reveals that there is not on file, nor has there ever been on file, an approved NDA or an IND for any of the drugs mentioned in paragraph 5(a) through (h) in the names of Generix Drug Corporation, Lewis Michael Orlove, Gary R. Dubin or Ofelia Perez.

7. Further, the search reveals that the following manufacturers who have supplied or have attempted to supply Generix Drug Corporation with the drugs named in 5(a) through (h) above do not now hold nor have they ever held, an approved NDA or an IND as follows:

Drugs	Source
5(a), (b), (c), (d), (e), (f) & (g)	Pharmadyne Laboratories Hackensack, New Jersey
5(h)	M. D. Pharmaceuticals Santa Ana, California
5(d)	Premo Pharmaceutical Labs. South Hackensack, New Jersey
5(g)	Generix International Div. Apotex Inc. Ontario, Canada Montreal, Quebec Vancouver, B.C.

8. In addition I have reviewed the brochure entitled "Goldline's Big Deal by Generix Drug Corporation" mentioned in paragraph 10 of the Complaint filed in this action. There are many drug products listed in this brochure which are regarded as new drugs by the United States Food and Drug Administration, e.g., phentermine, spironolactone, carisoprodal compound, cyproheptadine hydrochloride tablets, betamethasone valerate cream and trimethobenzamide. We are currently investigating to determine whether Generix is receiving these drugs from sources with approved NDAs.

/s/ Jerome A. Halperin
JEROME A. HALPERIN

State of Maryland)
County of Montgomery) ss

Subscribed and sworn to before me this 16th day of November 1979.

/s/ Anna M. Robertson
ANNA M. ROBERTSON
Notary Public
My Commission Expires July 1, 1982

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

No. 79-6655-CIV-NCR

UNITED STATES OF AMERICA, PLAINTIFF

vs.

GENERIX DRUG CORPORATION, a corporation, and LEWIS MICHAEL ORLOVE, and GARY R. DUBIN, and OFELIA PEREZ, individuals, DEFENDANTS

OPPOSITION TO GOVERNMENT'S MOTION FOR PRELIMINARY INJUNCTION

Defendants hereby oppose the Government's Motion for Preliminary Injunction in this matter, and submit in support of their opposition the following:

1. Memorandum in Support of Defendant's Opposition to Motion for Preliminary Injunction.
2. Affidavit of Kenneth I. Sawyer.
3. Affidavit of Emil R. Smith.

Testimony will be offered at the hearing in additional support of defendants' opposition.

/s/ Thomas Scarlett
THOMAS SCARLETT
Morgan, Lewis & Bockius
1800 M Street, N.W.
Washington, D.C. 20036
(202) 872-5096
Attorney for defendants

Date: January 11, 1980

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

No. 79-6655-CIV-NCR

UNITED STATES OF AMERICA, PLAINTIFF

vs.

GENERIX DRUG CORPORATION, a corporation, and LEWIS MICHAEL ORLOVE, and GARY R. DUBIN, and OFELIA PEREZ, individuals, DEFENDANTS

AFFIDAVIT OF KENNETH I. SAWYER

Kenneth I. Sawyer deposes and says:

1. I am Vice President and General Counsel of Generix Drug Corp., a position I have held since May 15, 1979. Prior to that time, I provided legal services to Generix as a member of a law firm that acted as counsel to Generix. I am a member of the bars of Florida and Pennsylvania and of the bar of this Court.

2. Generix Drug Corp. is a pharmaceutical company engaged in the business of distributing high quality generic drugs at reasonable prices. A generic drug is a drug with the same active ingredients as a brand name drug. The principal difference to the consumer between a brand name drug and a generic version of the same drug is that the generic drug costs considerably less than the brand name drug. By offering less expensive versions of commonly used drug products, Generix enables its customers to pass along cost savings to members of the public who must take those drugs. The price Generix charges to its customers is about one-half the price that is charged for the same drug under a brand name.

3. Generix does not manufacture drugs itself. Rather, Generix purchases drugs from manufacturers, and distributes them, under its own "Goldline" trade name, through Generix's marketing organization. Most of the

drugs supplied to Generix are in a form suitable for final distribution, i.e., packaged and labeled for marketing to Generix's customers. A small part of Generix's activities involves repackaging bulk supplies of drugs into final form. Generix distributes about 2000 drug products. About 20 of those products are involved in the repackaging operation. This aspect of Generix's business is regarded by the Food and Drug Administration (FDA) as a form of manufacturing.

4. As General Counsel to Generix, it is my responsibility to meet with representatives of the FDA with respect to FDA regulatory activities relating to Generix, to obtain from Generix's suppliers suitable assurances that drugs distributed by Generix comply with applicable legal requirements, to notify those suppliers of legal actions involving Generix that affect their drugs, and generally to coordinate Generix's legal affairs.

5. The Government's injunction action seeks to prohibit the sale of some of the drugs distributed by Generix. The Government's position is not based on any concern that the drugs are unsafe. Rather, it is based on FDA's belief that the drugs in question are "new drugs" that must be approved by FDA by way of a "new drug application" (NDA). Only drugs that are "new drugs" are required to have an NDA as a condition of marketing. Generix does not believe that the drugs mentioned by the Government in its pleadings are "new drugs." None of those drugs—indeed, no drug distributed by Generix—has been determined to be a "new drug" in a binding judicial or administrative proceeding. The drugs that Generix distributes are generic versions of drugs that have been marketed for many years, often for decades, under approvals granted by the FDA for brand name versions of those drugs. Since becoming General Counsel of Generix, it has been my practice, prior to the distribution of a drug by Generix, to contact the manufacturer of the drug to obtain assurances that the drug conforms to the requirements of the law. In many cases, I have engaged in such consultation with respect to drugs

that Generix began marketing prior to my becoming General Counsel. Generix thus distributes drugs in good faith reliance on representations of the drugs' manufacturers that the drugs meet applicable legal standards and are of high quality. It should be emphasized that a drug is not unsafe or of questionable quality simply because it has no NDA. All drugs are subject to provisions in the statute and FDA's regulations regarding good manufacturing practices, adulteration, and compliance with compendial standards for strength, quality, and purity.

6. The following is a list of the drugs mentioned in footnote three of the Government's memorandum. (Amitriptyline with perphenazine is omitted because Generix does not presently distribute that drug or have any immediate plans to do so.) These drugs are distributed in generic form by Generix. Next to each drug is the name of a brand name product containing the same active ingredient or ingredients, with the approximate year in which the brand name drug was first introduced into the market. (The year of introduction for most of the brands is derived from the International Marketing Survey: Prescription Survey for Leading Products for 1976-1977.)

Drug	Brand Name	Year
allopurinol	Zyloprim (Burroughs Wellcome)	1966
furosemide	Lasix (Hoechst-Roussel)	1966
chlorothiazide with resperine	Diupres (Merck Sharp Q Dohme)	1959
spironolactone with hydrochlorothiazide	Aldactazide (Searle & Co.)	1962
diethylpropion hydrochloride	Tenuate (Merrell-National)	1959
prochlorperazine maleate	Compazine (Smith Kline & French)	1956
chlorthalidone	Hygroton (USV)	1971
phentermine	Ionamin (Pennwalt)	1959
spironolactone	Aldactone (Searle & Co.)	1962
betamethasone valerate	Valisone (Schering)	1967
trimethobenzamide	Tigan (Beecham)	before 1962

7. Generix's business decision to distribute generic versions of these drugs, even though their manufacturers had not obtained an NDA for them, was based on certain legal developments. In 1978, a U.S. Court of Appeals decided that the generic versions of FDA-approved drugs are not considered "new drugs" simply because they are newly marketed as individual products. *United States* v. *Articles of Drug . . . Lannett Co.*, 585 F.2d 575 (3d Cir. 1978). In other words, a generic version of allopurinol—which has been sold for many years under a brand name—is not a "new drug" merely because the generic product itself has not been marketed for a substantial period of time. The Court of Appeals' interpretation of the meaning of "new drug" is the most authoritative interpretation of the law currently available for the guidance of drug manufacturers. Under that interpretation, the generic version of an FDA-approved drug may be legally marketed without an NDA if it is not within the legal definition of a "new drug." Whether a particular drug is a "new drug" depends, under the *Lannett* decision, on whether the active ingredient of the drug is not "generally recognized" among experts as "safe" and "effective." A determination that a drug is not generally so recognized is a factual one. If a drug is not generally recognized as safe and effective, then the drug requires an NDA approved by the FDA before it can be marketed. However, if a drug *is* generally recognized as safe and effective, then an NDA is not required, and a manufacturer may market the drug without FDA approval.

8. It was only after the *Lannett* decision that Generix decided to market some generic versions of brand name drugs in the absence of specific approval required by the FDA for the individual generic products. The drugs that Generix distributes contain the same active ingredients as well-known and widely-used brand name drugs. In other significant respects, such as labeling, dosage form, and strength, Generix's drugs also conform to the

brand name versions. Generix believes that the drugs whose distribution FDA is seeking to prevent are not "new drugs," and, therefore, that they do not require FDA approval prior to marketing. It is important to keep in mind that the manufacturers of these drugs also believe that their drugs are not "new drugs." Generix, as a distributor, sells drugs on the basis of the manufacturer's opinion that its drugs are in compliance with the law. Because Generix is a distributor, it is not in a position to obtain approval of an NDA for any of the drugs at issue in this lawsuit even if it believed that they were "new drugs."

9. None of the drugs now being marketed by Generix has been adjudicated to be a "new drug." The Government's pleadings in this injunction assert that Generix's products are "new drugs" based on FDA's position that every individual product is a "new drug" even though it is the generic version of a drug with substantial marketing experience whose safety and effectiveness are widely recognized. Conspicuously absent from the Government's trial memorandum is any mention of chlorporpamide as one of the drugs FDA regards as a "new drug." Generix distributes chlorpropamide, which is, like the other drugs in issue, regarded by FDA as a "new drug" whose manufacturer does not have an NDA. The reason for this anomaly would appear to be the fact that chlorpropamide was adjudicated to be *not* a "new drug" by a U.S. District Court, in a lawsuit brought by the drug's manufacturer, and one of Generix's suppliers, Premo Pharmaceutical Laboratories, Inc.

10. FDA refers to a number of legal actions relating to Generix's products. Those actions consist of Florida State "remove from sale" notices and FDA complaints for civil seizure. Both forms of action apply to specific lots of drug products regarded by FDA as in violation of the law. The Florida actions were all taken at FDA's request, and do not represent an independent initiative by the State. Even though under Florida law the State must take further action under a "remove from

sale" order within a reasonable time, in no case affecting Generix's drugs am I aware that Florida has done so. With respect to FDA's seizure actions (filed by the U.S. Attorney), Generix's practice is to notify the manufacturer of seized drugs that such an action is pending. The manufacturer may then defend the action or not, as it sees fit. It is my understanding that all FDA seizures of Generix drugs are in litigation at this time, except for several seized lots that have been defaulted. To my knowledge, no product that is the subject of such a seizure has been adjudicated to be a "new drug."

11. FDA asserts that one of Generix's drugs, chlorthalidone, is a "new drug," and that its status as a "new drug" cannot be relitigated because Generix had an opportunity to request a hearing on that question before the FDA. The notice that offered that opportunity proposed to withdraw approval of the 100 mg. dosage strength of that drug. 44 FR 54126 (Sept. 18, 1979). Other dosage strengths of chlorthalidone were found in that notice to be effective. Although I read the notice when it was issued, and even requested a hearing for Generix on the 100 mg strength (see attachment), it was not my understanding that an opportunity for a hearing was being offered on any drug other than the 100 mg strength of chlorthalidone. Under the statute and FDA's regulations, when FDA proposes to withdraw approval for a particular dosage strength of a drug, that dosage strength is treated as a separate drug for administrative purposes. The text of the FDA document stated that "notice is given to the holder of a new drug application [for chlorthalidone] and to all other interested persons" that FDA proposed to withdraw [*sic*] approval "of those parts of the new drug application providing for chlorthalidone 100-milligram tablets" on the ground that "the drug product is not shown to be safe for use." All subsequent references to products covered by the notice of opportunity for a hearing appear to relate back to the 100-mg product. As to the 50 mg dosage strength,

no notice of opportunity for a hearing on chlorthalidone's "new drug" status appears in the document relied on by FDA. In fact, in a letter from the FDA Compliance Officer for the Orlando District Office to the President of Generix, FDA advised Generix that when a Federal Register announcement is published in which FDA declares a drug to be effective—as was the case in the document for the lower dosage strengths of chlorthalidone—"drugs being marketed without an NDA are subject to regulatory action. There is no period of time allowed for the continued distribution of products in stock." The FDA letter made no reference to an opportunity for a hearing on the "new drug" status of products, and it is only if a drug is a "new drug" that an NDA is required for marketing.

12. The affidavit of FDA District Director Alan J. Trujillo states, in paragraph 10(i), that in a meeting with FDA officials I said that "the firm was not presently and would not in the future market drugs that are in violation of the law." Mr. Trujillo is evidently suggesting that I was not candid in my assertion on the ground that Generix subsequently marketed drugs that FDA regards as new drugs. As can be seen from the above, however, Generix does not agree, based on the *Lannett* decision, that those drugs are new drugs, and therefore the drugs were not "in violation of the law" as far as I was concerned.

13. Because of FDA's position that every drug product requires an NDA before it can be marketed, the pharmaceutical industry has become divided over the legal issue involved in this injunction suit. The larger manufacturers, especially the brand name manufacturers, tend to favor FDA's view that NDA's are required for all drugs. The NDA requirement is a barrier to entry into the drug market and FDA's legal position, by reducing competition, favors larger companies with existing NDAs over smaller companies who would need FDA approval before marketing competitive, and cheaper, versions of

the same drugs. Such approval is costly to obtain, and is frequently granted only after substantial administrative delays. I am advised that these delays are often on the order of several years. The losers in this tug of war are consumers, who must pay higher prices for brand name products unless a generic is available. In some cases, there is only one brand name version of a drug, and the only competition is provided by generic versions of the drug.

14. Generix does no manufacturing. It obtains the drugs it distributes from companies engaged in the drug manufacturing business. Premo Pharmaceutical Laboratories, Inc. and Pharmadyne Laboratories, Inc., are two of Generix's suppliers. They have been involved in several court cases in which the "new drug" status of their drugs was at issue. FDA's injunction action against Generix, therefore, appears to be part of a more general plan to prevent the manufacture and sale of generic drugs not approved by FDA by cutting off the channels of distribution used by the manufacturers of those drugs, rather than by suing the manufacturers directly. Generix is only one of a number of companies engaged in the distribution of such drugs in significant volume. Some of the other distributors are Henry Schein, Inc., Mason Distributors, Inc., Crown Drug Co., h.1. Moore Drug Exchange, Modern Wholesale Drug Co., Inc., Gulfcoast Drug Supply, Inc., Spencer-Mead, Inc., Parmed, D.A. Risow, and J.J. Balin. If FDA is correct that the drugs at issue in this case cannot be legally marketed without FDA approval, the agency could terminate such marketing more effectively by suing the producers of the drugs than it can by proceeding against one distributor—Generix. This is so because an injunction against Generix will not prevent the drugs from being produced by the manufacturers. Based on my experience in the generic drug business, if Generix is unable to supply a particular drug, those who wish to purchase it will seek out another distributor. In other words, the drug itself will

continue to be sold even if Generix is unable to distribute it.

15. FDA believes that its NDA approval system for all drug products is beneficial to public health. However, FDA had not been able to make out a credible case that marketing of generic drugs without prior approval represents a public health problem, other than by speculating that something might go wrong with a generic drug unless FDA evaluated it first. Generic drugs, however, are fully subject to other aspects of the Federal Government's drug regulation system, such as FDA's requirements for good manufacturing practices, detailed labeling standards, and the compendial standards of the United States Pharmacopeia, which are designed to assure that all drugs are of adequate strength, quality, and purity.

16. It should be emphasized in this regard that none of the drugs that FDA contends are "new drugs" are presently involved in the operations of Generix alleged to be inconsistent with FDA's GMP regulations. The GMP allegations relate to Generix's limited repackaging business. Generix has not repackaged any drug referred to by FDA in its injunction papers for nearly a year.

17. Generix employs about 200 people. Although Generix sells generic drugs that have FDA-approved NDAs, a substantial portion of its current sales consists of drugs that do not have approved NDAs. Generix is interested in operating a profitable business. However, Generix's business can be profitable only if it sells a quality product at a reasonable cost. It is the right to engage in that business that Generix seeks to protect against FDA's contention that Generix's products are unlicensed "new drugs." Generix would suffer significant financial losses if it were enjoined from distributing the generic drugs FDA contends are "new drugs." Generix would incur even more serious losses if it were required to recall all of the drugs that FDA regard as "new drugs," as the Government demands. It makes no sense to impose these

severe consequences on Generix when the only result will be that *other* distributors will continue to see the *identical* drug of the *identical* manufacturers to the *identical* customers.

I hereby certify under penalty of perjury that the foregoing statement is to the best of my knowledge true and correct.

/s/ Kenneth I. Sawyer

Signed this 7th day of January, 1980.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

No. 79-6655-CIV-NCR

UNITED STATES OF AMERICA, PLAINTIFF

vs.

GENERIX DRUG CORPORATION, a corporation, and LEWIS MICHAEL ORLOVE, and GARY R. DUBIN, and OFELIA PEREZ, individuals, DEFENDANTS

AFFIDAVIT OF EMIL R. SMITH

Emil R. Smith deposes and says:

1. I am the Acting Chairman of the Department of Pharmacology of the University of Massachusetts Medical School in Worcester, Massachusetts. I assumed that position on July 1, 1979. Since 1975, I have been an Associate Professor in the same Department. I hold M.S. and Ph.D. degrees in pharmacology from Tufts University. I am currently a member of the American Society for Pharmacology and Experimental Therapeutics and the Society for Toxicology. I have been a pharmacologist for nearly 25 years. A copy of my curriculum vitae is attached.

2. My area of professional expertise is pharmacology. Pharmacology is the science that deals with the interaction of chemicals and living systems. The body of knowledge involved in pharmacology includes broad familiarity with the major drugs in use in the United States, and with the types of scientific studies regarded by experts as reliable evidence of the safety and effectiveness of drugs.

3. Before joining the faculty of the University of Massachusetts Medical School, I held a number of positions in private industry. My experience in those positions included designing and participating in the execu-

tion of adequate and well-controlled clinical investigations of prescription drugs in humans. A number of the studies in question were submitted to, and accepted by, The Food and Drug Administration as support for the approvability of new drug applications. I was, in fact, personally responsible for preparing the safety and effectiveness sections of several of these new drug applications for submission to the FDA. Several of the studies for which I was responsible have been published in the scientific literature.

4. By reason of my educational background and professional experience, I am generally familiar with the scientific and medical reputation for safety and therapeutic effectiveness of most of the important drugs in use today. Although I am not a physician, I teach the subject of drug therapy to medical students, and I advise medical doctors on the proper use of drugs in the treatment of disease. I attend medical rounds and discuss questions of drug therapy with physicians and medical students. I was recently involved in establishing a clinical pharmacology program at the Medical School. My teaching and other duties require that I keep current in my field. I do this by reading scientific publications, by attending meetings and conferences on drug-related subjects, and by exchanging information and views with other professionals active in my area of interest. As a result of these activities, I am aware of the consensus of opinion in the scientific community concerning whether the drugs under consideration in this lawsuit are safe and effective for their intended therapeutic uses, and I am also able to evaluate the state of scientific and medical opinion concerning those drugs based on material available in the current literature relevant to drug safety and effectiveness.

5. I have been asked to give my opinion concerning whether the drugs involved in this lawsuit are, or are not, "generally recognized, among experts qualified by scientific training and experience to evaluate the safety

and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling" of the drugs, and whether those drugs have, or have not, been used "to a material extent or for a material time." The quoted words are from the definition of a "new drug" in the Food, Drug, and Cosmetic Act. My opinion, however, involves strictly a factual assessment of whether the drugs in question are "generally recognized" as safe and effective and have been used to a material extent and for a material time. The labeling I have used in arriving at my opinion is the labeling provided with the product distributed by Generix Drug Corp. that contains the drug, or drugs, to which my opinion relates. I have reviewed the Generix labeling and verified that it corresponds with the labeling of the brand name counterpart of the drug in question. In evaluating whether a drug is "generally recognized" as "effective," I have considered whether there is published material on the drug meeting the "substantial evidence" definition of 21 U.S.C. § 355(d). "Substantial evidence" is defined as "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof."

6. The drugs, or combinations of drugs, I have considered are:

allopurinol
betamethasone valerate
chlorthalidone
diethylpropion hydrochloride
furosemide
phentermine
prochlorperazine maleate

spironolactone
trimethobenzamide
chlorothiazide with reserpine
spironolactone with hydrochlorothiazide

7. Based on my knowledge and experience as a pharmacologist and based on my review of the relevant scientific and medical literature, it is my opinion that each of the above drugs, or combinations of drugs, is "generally recognized" among qualified experts as safe and effective, and that each has been used to a material extent and for a material time, for the uses recommended in the labeling employed by Generix. There is one drug with respect to which my opinion is somewhat qualified—chlorothiazide with reserpine. This will be further discussed below.

8. The following sources of information were consulted as the basis for my opinion that the drugs are generally recognized as safe and effective and have been marketed to a material extent and for a material time:

a) Goodman and Gilman: *The Pharmacological Basis of Therapeutics* (1975). This is the principal textbook of pharmacology.

b) Drug Compendia. Three compendia were consulted: The United States Pharmacopeia (19th ed., 1975); The National Formulary (14th ed., 1975); Martindale, *The Extra Pharmacopeia* (27th ed. 1977).

c) The AMA Drug Evaluations (3rd ed. 1977).

d) The University of Massachusetts Medical Center (UMMC) Formulary for 1979-1980.

e) MEDLINE, a computer-based search of Index Medicus for 1967-January 1980, Hospital Literature Index for 1967-January 1980, and selected monographs. In addition, some standard pharmacological reference works were consulted. In connection with my review, I examined several hundred reports of clinical investigations.

f) Materials published by International Marketing Survey (for dates of initial marketing and extent of marketing) and Pharmacy Times (for extent of marketing).

The following briefly summarizes the basis for my opinion as it relates to each drug. (The figure in parentheses after the name of each drug refers to the ranking of *one brand* of the drug in total dollar sales volume in the United States in 1978. To provide a perspective on the extent of marketing of these drugs, of those discussed in this affidavit, the highest-ranked drug in 1976—the Lasix brand of furosemide—had a sales volume of over $53 million in that year, and the lowest-ranked—the Diupres brand of chlorothiazide with reserpine—had a sales volume of over $7 million in 1976.)

allopurinol (60. Since its initial marketing in 1966, allopurinol has been widely used for the treatment of gout, uric acid nephropathy, recurrent uric acid kidney stone formation, and for the prevention of tissue urate deposition, renal calculi or uric acid nephropathy in patients receiving cancer chemotherapy. Its pharmacology is described in some detail in Goodman and Gilman. It is listed in the United States Pharmacopeia, the AMA Drug Evaluations, and the UMMC Formulary. There is an extensive published literature concerning its use in man, including adequate, well-controlled studies demonstrating its effectiveness.

betamethasone valerate (70). This glucocorticoid has been marketed since 1967 and finds wide use for the relief of inflammatory manifestations of corticosteroid-responsive dermatoses. Its pharmacology and use are discussed in Goodman and Gilman and in the AMA Drug Evaluations. It is listed in the National Formulary and in the UMMC Formulary. There is an extensive published literature on the clinical pharmacology of betamethasone and many published studies, including well-controlled studies, on the effects of betamethasone valerate on cutaneous lesions in man.

chlorthalidone (31) This oral antihypertensive and diuretic agent has been marketed since 1971. Its pharmacology is described in Goodman and Gilman and in the AMA Drug Evaluations. It is listed in the U.S. Pharmacopeia and the UMMC Formulary. Both its antihypertensive and diuretic (edema mobilizing) effects have been well-documented by well-controlled studies in man.

diethylpropion hydrochloride (86). This drug has been marketed since 1959 as an anorexiant (appetite suppressant) for use as an adjunct in treating obesity. It is listed as an "anorectic" in Goodman and Gilman. The pharmacology of diethylpropion hydrochloride and related amphetamine-like agents is particularly well described in the AMA Drug Evaluations. There is a reasonably extensive published literature on this subject, and it includes several well-designed and well-controlled studies on the use of diethylpropion in the treatment of obesity in man.

furosemide (4). This substance has been very widely used to treat hypertension and edema since its introduction in 1966. In fact, it is one of the most widely-used drugs in the United States. Its pharmacology and therapeutic uses are described in Goodman and Gilman and in the AMA Drug Evaluations. It is listed in the U.S. Pharmacopeia and in the UMMC Formulary. Furosemide has been the subject of a large number of well-controlled and well-executed clinical trials that have documented its effectiveness and safety for the treatment of hypertension and edematous states.

phentermine (114). First marketed in 1959, phentermine is an amphetamine-like anorectic agent that is used as an adjunct to the treatment of obesity. Its pharmacology is described in Goodman and Gilman and in the AMA Drug Evaluations. It is listed in Martindale's Pharmacopeia. The efficacy and safety of phentermine in the treatment of obesity have been the subject of well-controlled, well-executed studies in man.

prochlorperazine maleate (98). This substance is used in the management of the manifestations of psychotic disorders; management of psycho-neurotic patients displaying anxiety and tension; and for the control of severe nausea and vomiting. It has been widely used for these purposes since first marketed in 1956. The pharmacology and clinical utility of this substance and related substances are described by Goodman and Gilman and in the AMA Drug Evaluations. It is listed in the U.S. Pharmacopeia and the UMMC Formulary. The clinical uses of prochlorperazine for the management of psychotic patients and to control nausea and vomiting have each been the subject of several well-controlled and well-executed studies.

spironolactone (147). Spironolactone is a specific pharmacological antagonist of the action of the hormone aldosterone. By virtue of its ability to block the actions of aldosterone, spironolactone has proven to be of value in the treatment of primary hyper-aldosteronism and in the treatment of a variety of edematous conditions. Spironolactone has been widely used for these purposes since its introduction into the marketplace in 1962, and its clinical pharmacology is described in both Goodman and Gilman and the AMA Drug Evaluations. It is listed in both the U.S. Pharmacopeia and the UMMC Formulary. Spironolactone has been the subject of extensive clinical investigations in man. These include several studies documenting its safety and efficacy in the treatment of hyperaldosteronism and edematous states, including well-controlled and well-executed studies.

trimethobenzamide (152). This substance has been used in the U.S. since at least 1962 as an antiemetic (antivomiting) drug. The pharmacologic properties of this and related substances are particularly well described in the AMA Drug Evaluations and trimethobenzamide is listed in the National Formulary and the UMMC Formulary. The antiemetic effects of trimethobenzamide in man have been documented in several well-designed and well-controlled clinical trials in the U.S.

chlorothiazide-reserpine (196). Since 1959 a fixed-combination product containing both chlorothiazide and reserpine has been marketed in the U.S. and widely used for treating hypertension. While Goodman and Gilman, the U.S. Pharmacopeia, and the National Formulary do not generally list or discuss the pharmacology of fixed combination products, these sources do separately list and/or describe the separate drug substances chlorothiazide and reserpine, as both are well-known and widely-used drugs. In addition, the combination of chlorothiazide and reserpine is discussed in the AMA Drug Evaluations. The effective and safe treatment of hypertension by combining chlorothiazide and related thiazide diuretics with reserpine and related rauwolfia alkaloids is well-documented in the published literature, although studies on the specific combination of chlorothiazide with reserpine have not been found in my initial examination of the published literature. Studies do exist in which chlorothiazide and reserpine were both administered to the same patients, but not in the form of a fixed combination of drugs.

spironolactone-hydrochlorothiazide (52). This fixed combination of drugs has been very widely used in the treatment of edematous conditions and essential hypertension since first marketed in 1962. The usefulness of this combination is discussed in the AMA Drug Evaluations, and the drug is listed in the UMMC Formulary. The individual drug substances, spironolactone and hydrochlorothiazide, are discussed in the U.S. Pharmacopeia and in Goodman and Gilman, although the specific combination is not. Well-designed, well-controlled studies on the diuretic and antihypertensive effects of this combination in man have been published in the medical literature.

9. My opinion that each of these drugs is "generally recognized" as safe and effective and has been used to a material extent and for a material time relates to the drugs as drug substances. (A "drug substance" is, in effect, the "active ingredient.") In other words, I have

not considered whether a particular product containing a given drug substance, or combination of drug substances, is "generally recognized." Rather, I have determined only that the drug substances themselves have achieved widespread acceptance in the medical community, without regard to the manner in which they are formulated by different drug manufacturers.

10. It is my opinion that the "general recognition" standard cannot be applied in a meaningful way to a specific drug product. The "general recognition" test requires that evidence of the safety and effectiveness of a drug be widely available to experts, particularly in the form of published studies. To the extent that the particular product formulation of an active drug ingredient is relevant to safety and effectiveness, the relevance pertains to characteristics of the product that are rarely, if ever, noted in the published literature. Included among the characteristics that may vary among different products are: the inactive ingredients used in a product; the manufacturing techniques used to produce a product; and the bioavailability and bioequivalence of a product. ("Bioavailability" refers to the rate and extent of absorption of a drug; "bioequivalence" refers to comparison of the biological effects of the same drug substance in different drug products.) It is true that all of these characteristics can affect how a drug product performs, and can therefore be said to play a role in the safety and effectiveness of the drug. However, it is also true that the scientific consensus that a drug is safe and effective remains the same regardless of differences among specific drug products. In other words, it would be possible to formulate allopurinol in a product in such a way that the allopurinol would never be released. Under those circumstances, the product would be completely ineffective, but the drug —allopurinol—would still be regarded as effective.

11. Experts in drug evaluation are usually aware, of course, that different products containing the same active drug ingredients sometimes perform differently, and

they generally are aware of the factors that cause those differences (e.g., differences in bioavailability, in the inactive ingredients used, and in the way in which the product is manufactured). But those experts often do not have access to the data on specific drug products, or do not avail themselves of such data; and in the process of evaluating the safety and effectiveness of a drug substance (i.e., the active ingredient), they either are not in a position to take product-specific data into account in reaching a conclusion about the safety and effectiveness of a drug, or choose not to make the distinction between the drug and the drug product. Moreover, product-specific information relating to inactive ingredients, bioavailability, and manufacturing processes is generally not available in the scientific literature. In fact, in the published studies on the safety and effectiveness of a drug, the investigator often does not even mention the brand name of the product used in the study.

12. In that regard, I should point out that inadequate performance by a drug product can be the result of a variety of factors. I am aware of product failures involving both brand name drugs and generic drugs.

I hereby certify under penalty of perjury that the foregoing statement is to the best of my knowledge true and correct.

/s/ Emil R. Smith
EMIL R. SMITH

Dated: Jan. 10, 1980

SUPREME COURT OF THE UNITED STATES

No. 81-1222

UNITED STATES, PETITIONER

v.

GENERIX DRUG CORPORATION, ET AL.

ORDER ALLOWING CERTIORARI

Filed March 1, 1982

The petition herein for a writ of certiorari to the United States Court of Appeals for the Eleventh Circuit is granted.

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Opposition

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CLERK

NO. 81-1222

in the

Supreme Court

of the

United States

OCTOBER TERM, 1981

UNITED STATES OF AMERICA,
Petitioner,

vs.

GENERIX DRUG CORPORATION, *ET AL.*,
Respondents.

On Petition for a Writ of Certiorari to The United States Court of Appeals For the Eleventh Circuit

BRIEF IN OPPOSITION

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QUESTION PRESENTED

Whether all generic drug products, including over the counter products, require premarket approval by the FDA when they contain active ingredients which are generally recognized as safe and effective?*

*Respondents adopt and incorporate the statement of parties contained in Petitioner's brief at I.

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NO. 81-1222

in the Supreme Court of the United States

OCTOBER TERM, 1981

UNITED STATES OF AMERICA,
Petitioner,

vs.

GENERIX DRUG CORPORATION, *ET AL.*,
Respondents.

On Petition for a Writ of Certiorari to The United States Court of Appeals For the Eleventh Circuit

BRIEF IN OPPOSITION

Respondents Generix Drug Corporation, Lewis Michael Orlove, Gary R. Dubin and Ofelia Perez oppose the petition for writ of certiorari filed by the Solicitor General on behalf of the United States.[1]

[1]Petitioner United States will be referred to as the "Government." Respondents will be referred to collectively as "Generix." "R" refers to the district court record as transmitted to the court of appeals. "T" refers to the transcript of the hearing in the district court on the Government's motion for a preliminary injunction.

Generix adopts the Opinions Below, Jurisdiction and Statutes Involved sections of the Government's petition. This brief is a response to the Government's arguments on jurisdiction. It is not a comprehensive response to the Government's arguments on the ultimate merits of the case.[2]

STATEMENT OF THE CASE

Generix is a pharmaceutical company engaged in the business of distributing[3] high quality generic drugs at reasonable prices. A generic drug is a drug with the same active ingredients as a brand name drug. All of the drugs that Generix distributes are generic formulations of drugs which have been marketed for many years, often for decades, under approvals granted by the FDA for brand name versions of those drugs. The principal difference to the consumer between a brand name drug and a generic version of the same drug is that the generic drug costs considerably less than the brand name drug. Generix' drugs cost approximately one-half the price that is charged for the same drug under a brand name. (R. 197).

The Government filed suit seeking to prohibit the sale of some of the drugs Generix distributes. The Government did not take the position or adduce any

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[2]For this reason, Generix requests that it be given an opportunity to submit a brief on the merits and to present oral argument if this Court grants the petition.

[3]Generix does not manufacture the drugs it sells. It obtains them from pharmaceutical companies which specialize in making generic versions of brand name drugs. (R. 198).

evidence to show that Generix' drugs were unsafe. Rather, the FDA's position was that the drugs were "new drugs" under 21 U.S.C. § 321(p) which required approval by the FDA by way of a "new drug application" ("NDA").[4] Only drugs that are new drugs under 21 U.S.C. § 321(p) require an NDA as a condition of marketing.[5]

The pharmaceutical industry is divided over the legal issue involved in this suit. The NDA requirement is a barrier to drug market entry. Approval is costly to obtain and is frequently granted only after substantial administrative delays. NDA proceedings can take several years. The FDA's position, by reducing competition, favors larger companies, especially the brand name manufacturers with existing NDAs, over smaller

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[4]The complaint also alleged that Generix had violated certain "current good manufacturing practices" ("CGMPs"). (R. 3-5). The issue of the alleged CGMP violations was resolved by the parties during the hearing on the motion for preliminary injunction. (T. 186-87).

[5]The Government has phrased the issue before this Court as relating only to prescription drugs. But the new drug definition does not distinguish between prescription and over-the-counter (OTC) drugs. The FDA has adopted regulations under which OTC drugs are classified as "generally recognized" as safe and effective, and can be marketed without NDA approval, if they meet the standards applicable to generic classes of OTC drugs (such as analgesics and laxatives). *See* 21 C.F.R. § 330.10. In addition, OTC drugs must contain only approved active ingredients, be manufactured in accordance with the CGMPs, be properly labeled and contain "suitable" inactive ingredients. *See* 21 C.F.R. § 330.1. If the "new drug" definition applies to specific products, the agency's approach to OTC drugs is illegal. Although the FDA's diametrically opposed systems for OTC and prescription drugs may be administratively convenient, they cannot be reconciled on legal or theoretical grounds.

companies which would need FDA approval before marketing competitive and cheaper versions of the same drugs. The losers in this tug-of-war are consumers, who must pay higher prices for brand name products unless a generic is available. In some cases, there is only one brand name version of a drug and the only competition is provided by generic versions of the drug. (R. 204-05).

At the hearing on the preliminary injunction, the Government introduced evidence concerning the following drugs: allopurinol, spironolactone with hydrochlorothiazide, furosemide, diethylpropion hydrochloride, chlorothiazide with reserpine and amitriptyline with perphenazine. (R. 379).[6] Each of these drugs is marketed under a brand name formulation which has an NDA. (R. 199). All of these active ingredients are generally recognized among qualified experts as safe and effective. Each has been used to a material extent and for a material time for the uses recommended in the labeling employed by Generix. (R. 212-24). Each drug has been widely used and is well known although

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[6]The Government did not introduce any evidence concerning prochloreperazine maleate or chlorthalidone. (R. 379). Generix was not enjoined from distributing these drugs. (R. 388). The trial court named some drugs incorrectly in its preliminary injunction and enjoined distribution of specific products which already had ANDAs. Generix sought alternative relief in the form of modification of the preliminary injunction on these grounds on appeal. The Government did not oppose this request. The Eleventh Circuit did not reach the modification issues. If this Court grants certiorari and reverses the Eleventh Circuit, remand for consideration of this issue would be appropriate.

studies on the specific combination of chlorothiazide with reserpine are not readily available. (R. 212-24).[7]

The Government did not introduce evidence that the formulations of these drugs which Generix distributes are unsafe. It did not even introduce evidence that the generic formulations were different than the brand name formulations. Rather, the Government limited itself to showing that Generix' specific formulations containing these active ingredients had not been tested and were not generally recognized among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs as safe and effective under the conditions of use prescribed, recommended or suggested in Generix' labeling. *E.g.*, (R. 49-50).[8] Generix' expert testified to the contrary. (T. 227). Moreover, he testified that expert opinions about whether a drug is safe and effective "invariably reflect" an opinion on the active ingredient in the drug and not on the product itself since the experts do not have manufacturing information. (T. 212-13). Even the Government expert admitted that if it were necessary for the community of experts to have specific information about the way a

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[7]Contrary to the Government's implication, Generix did not argue that an NDA was not required merely because the brand name products had NDAs. It claimed that it was exempt from the NDA requirement because the active ingredients in its products were generally recognized as safe and effective.

[8]This testimony was circular. Government experts testified that Generix' drugs were not generally recognized as safe and effective because the specific formulations did not have FDA approval. (T. 60). Conversely, they recognized drugs as safe and effective simply because they had FDA approval. (T. 63).

particular drug product was manufactured before it concluded that the drug was safe and effective, most drug products would not be recognized as safe and effective. (T. 62-64).

The Government also introduced evidence about the manner in which drugs are formulated. A drug product is composed of an active ingredient, or incipient, which represents up to 10% of the product, and excipients, such as binders, coating and capsules, which account for the remainder. Variances in the excipients can affect the bioavailability of the active ingredient and the bioequivalence of the various drug products. (R. 380).[9] The Government experts testified that differences in bioavailability and bioequivalence between an approved drug and a generic copy may affect the safety and efficacy of the generic. (R. 380-81). However, there was no evidence that any differences between the approved drugs and the Generix formulations which were the subject of this proceeding made the Generix formulations unsafe or ineffective. (T. 72).[10]

There are various mechanisms in the law designed to deal with this problem. (T. 214). The United States

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[9]Bioavailability is a measure of the time it takes for a given drug product to deliver the active ingredient to a particular organ or area of the body. 21 C.F.R. § 320.1(a). Bioavailability is affected by inactive ingredients and manufacturing techniques, among other things. Bioequivalence is a measure based on a comparison of one drug with another. Drug products which are bioequivalent can be used interchangeably for the treatment of the same condition or illness. (R. 380).

[10]This logically followed from the Government's failure to show that there were any differences at all.

Pharmacopoeia and National Formulary contain standards to guarantee the identity, strength, quality and purity of drugs that are listed in them. (T. 215). All of the drugs in this case are listed in the United States Pharmacopoeia and National Formulary. (T. 215). These standards relate to how to get the drug substance into the body. (T. 215). If a drug does not meet these criteria, it is considered adulterated. (T. 216). The FDA has the power to regulate the sale of adulterated drugs. (T. 155-56).[11]

After reviewing the evidence, the trial judge rejected the Government's position that an NDA is required for each new generic drug product. He rejected Generix'

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[11]On October 20, 1981, the USP Advisory Panel to the Commission on Federal Drug Approval Process published an interim report critical of the stance which the FDA had taken in recent years concerning generic drugs. It pointed to the untoward delays in the processing of paper NDAs and ANDAs for duplicate drugs. It stated that possible health or safety problems could be handled by compendial standards and CGMP requirements rather than the NDA process. The panel concluded:

> We realize that our recommendations fly in the face of major efforts by FDA in recent years to build up case law supporting FDA controls over premarketing of every strength and every dosage form of *every* drug no matter how long similar products have been marketed by other companies or even by the same company. Yet when the total FDA manpower investment required and the cost to both the companies and to FDA are judged against the benefits of faster processing of New Drugs and the cost of improving the compendial-CGMP-inspection process, this appears to our Panel to be a *major* opportunity for FDA to improve its operations overall.

Id. at 3.

position that no generic drug is a "new drug" requiring FDA approval if the active ingredient is generally recognized as safe and effective. He ruled that a generic drug manufacturer is entitled to sell a generic drug without FDA approval if the evidence shows no reasonable possibility that differences in the excipients between a recognized and a generic product will make the generic product less safe and effective than the recognized product. He found that the Government had demonstrated a reasonable possibility that differences between certain Generix drugs and brand name drugs might affect the safety and effectiveness of the Generix drugs. He enjoined Generix from distributing products which contained six active ingredients. (R. 377-88).

Generix appealed. It argued on the basis of the Act, the legislative history and the FDA's own prior interpretation of the Act that a drug was not a new drug if it contained active ingredients which were generally recognized as safe and effective.[12] The Eleventh Circuit agreed with Generix. *United States v. Generix Drug Corp.*, 654 F.2d 1114 (5th Cir. 1981). It held that a drug product is not a new drug if the active ingredients

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[12]Premo Pharmaceutical Laboratories made this argument in its case in the district court. The district judge rejected the claim and ruled that "where the active ingredients in the brand name and generic products are identical but the excipients differ, the generic is not a new drug if the excipients are generally recognized as safe and there is no evidence that the excipients make the generic less safe or effective than the recognized product." *Premo Pharmaceutical Laboratories, Inc. v. United States*, 629 F.2d 795, 800 (2d Cir. 1980). The Government appealed and presented the same argument it presents here. Premo defended the trial court's position as appellee but did not cross appeal the trial court's refusal to accept the argument it had made in the trial court.

in the product satisfy the requirements of 21 U.S.C. § 321(p). The court based its decision on several factors. First, it relied on the plain words of the statute and the interplay between 21 U.S.C. §§ 321(g)(1) and (p). The court correctly reasoned that § 321(p) would be totally superfluous if, as the Government claimed, all drug products containing the same active ingredients were "new drugs." It reviewed the legislative history of the 1938 Act and the 1962 amendments. The court found that the FDA's interpretation of the Act would create a product-by-product licensing system, a conclusion which was against clear Congressional intent.

Generic drugs were not mentioned by name in the 1938 Act. But they played an extensive role in the 1962 amendments. The Government plays down the legislative history to the 1962 amendments and states that Congress "assumed that no drug would reach the market unless its safety and effectiveness were established through general recognition or an approved NDA." Government's brief at 17. The history belies this claim. As the Eleventh Circuit noted, the history specifically identifies three ways in which the safety and effectiveness of generic drugs could be regulated: (1) the registration of factories; (2) factory inspections; and (3) the adulteration provisions. 654 F.2d at 1119. Notably absent from the extended discussion of the means by which the safety and effectiveness of generic drugs could be regulated is any mention of the NDA requirement. The court concluded that the statute and its legislative history mandated the conclusion that "new drug" as used in § 321(p) applies only to the active ingredients in a drug product.

REASONS FOR DENYING THE WRIT

Generix does not dispute two of the Government's arguments. The decision here conflicts with the Second Circuit's decision in *Premo Pharmaceutical Laboratories, Inc. v. United States*, 629 F.2d 795 (2d Cir. 1980). The issue is of great public interest to all consumers of drugs. Generix does dispute the Government's conclusion that the issue should be resolved by this Court in this case. The Eleventh Circuit was correct. The bioavailability and bioequivalence issues about which the Government expresses concern were never considered by Congress when it passed the Federal Food, Drug and Cosmetic Act or the 1962 amendments. The alleged problems which the Government emphasizes are countered by competing considerations involving the public's access to affordable products. The courts of appeal which have considered the issue have reached different legal conclusions in large part because the cases were presented on different facts and different legal theories. In light of new developments in the scientific areas involved, legislation has been proposed which would adopt the licensing approach urged here by the Government. Congress, rather than the courts, should be given an opportunity to reconcile the competing interests involved.

Concerns about bioavailability and bioequivalence between products are of relatively recent vintage. The undersigned is not aware of any mention of the terms or concepts in the statute or the legislative history of the Federal Food, Drug and Cosmetic Act through the most recent major amendments to the Act in 1962. The Government has not cited any references.

The Government disingenuously for the first time in these proceedings relies on the history of the 1938 Act in support of its position. It claims that the Elixir Sulfanilamide incident which in part prompted enactment of the premarket clearance standard is analogous to the situation here by arguing that the chemical which caused the deaths in that incident, diethylene glycol, was an *inactive* ingredient. The Government's argument is a straw man. A lethal chemical is not an inactive ingredient.[13] The legislative history never refers to it as such. H.R. REP. NO. 2139, 75th Cong., 3d Sess. 9 (1938); S. DOC. NO. 124, 75th Cong., 2d Sess. (1937). The Government has never presented proof or even claimed that the excipients at issue are dangerous. Its only focus has been on differences in bioavailability and bioequivalence which may occur in different products with different excipients. The 1938 Act does not address the issue here.[14]

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[13]Diethylene glycol is the active ingredient in antifreeze. It is also used as a lubricating and finishing agent for certain fabrics and as a solvent in vat dyes. The Merck Index, An Encyclopedia of Chemicals and Drugs at 3091-92 (9th ed. 1976).

[14]The Government emphasizes the definition of drug in 21 U.S.C. § 321(g)(1). The Eleventh Circuit cited this section in its opinion. However, the Eleventh Circuit properly viewed this part of the statute in pari materia with 21 U.S.C. § 321(p) and the evidence the Government presented in the trial court. 21 U.S.C. § 321(p) provides that a drug is not a new drug if it is recognized by experts as safe and effective. However, even the Government's expert here conceded that only the active ingredient and not the product itself usually achieves general recognition. (T. 62-64). Moreover, if every drug product needs an NDA, 21 U.S.C. § 355 becomes superfluous since there are no products left which are "not new drugs." The Government attempts to counter this problem in its

The 1962 amendments to the Act belie the Government's position and its reliance on the original Act. Generic drugs were discussed extensively for the first time in the legislative history accompanying those amendments. Generix agrees with the Government that the 1962 amendments were not designed to weaken the Act. But neither did they require premarket clearance for generic drugs.

The legislative history of the 1962 amendments to the Act shows that Congress' paramount concern was the excessive cost of prescription drugs. [1962] U.S. CODE CONG. & AD. NEWS 2884-2936. Congress' primary goal was to reduce prices.

The legislation originated as the result of an investigation conducted by the Senate Subcommittee on Antitrust and Monopoly. The subcommittee found that the major drug companies made apparently unconscionable profits:

> These "extraordinary margins and profits" were attributed to the "tight control of the market in the hands of a few large companies" which resulted in rigid price structures over long

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(Footnote 14 Continued)

brief at 15, n. 24. It argues that a drug product can achieve "not new drug" status under § 355 "at some point after being marketed for a period of time in accordance with an NDA." In effect, the Government urges that a product which is required to have an NDA before marketing can achieve "not new drug" status and therefore not need an NDA after marketing. This argument does not make sense. The Eleventh Circuit properly construed the sections of the Act to give logical effect to all parts.

> periods of time. The subcommittee found that one of the principal factors underlying this market control was the success of major drug companies in persuading physicians to prescribe drugs by the companies' trade names despite the existence of less expensive, chemically identical generic-named drugs.

Note, *Drug Amendments of 1962—Generic Name Prescribing: Drug Price Panacea*, 16 STAN.L.REV. 649, 651-52 (1963-64). The legislation was designed to encourage generic-name prescribing and lower prices.

> The impetus for generic-name prescribing was to be created by provisions (1) assuring physicians that any drug sold in the United States, whether made by a large well-known manufacturer or a small, obscure one and whether sold by trade or generic name, would be of adequate and acceptable quality and (2) simplifying generic names and bringing them to the physician's attention.

Id.

Three specific sections of the legislation were to insure the quality of generic drugs.

> The first requires that every "establishment in any State engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs" register with the Secretary of Health, Education and Welfare. . . . The second section requires the FDA to inspect every establishment registered

> with the Secretary at least once every two years. . . . The third section requires adequate manufacturing safeguards and allows the FDA to seize drugs which have been manufactured without adequate safeguards even though their essential characteristics are unimpeachable.

Id. at 654-55. As stated in S. REP. NO. 1744, 87th Cong., 2d Sess. (1962):

> Section 5 of the bill, as amended, is intended to give the Food and Drug Administration additional authority to require that sound methods, facilities, and controls be used in all phases of drug manufacture and distribution. By an amendment of section 501(a)(2) of the Food, Drug, and Cosmetic Act, a drug would be deemed to be "adulterated" if such methods, facilities or controls were found not to conform to current good manufacturing practice to assure safety, identity, strength, quality and purity of the product.
>
> * * * *
>
> This section, together with the registration and factory inspection provisions of sections 3 and 4 of this amended bill, would greatly increase the Food and Drug Administration's authority over drug manufacture and distribution. These provisions should prove helpful in reaching persons who are responsible for putting drugs

of questionable or unknown quality on the market.

[1962] U.S. CODE CONG. & AD. NEWS at 2884, 2890.

The import of this history is clear. Congress intended to provide a mechanism by which the FDA had control over the formulation of generic drugs. But the mechanism was the adulteration provisions of the statute, not the NDA requirement.

Again and again in the legislative history, Congress indicated its intent that generic drugs should be used to a greater degree and that the means for insuring the safety and effectiveness of the generics were the registration, inspection and adulteration provisions of the statute, not a licensing or NDA requirement:

> MR. HART. One of the purposes of the bill is to bring about conditions under which doctors may prescribe drugs by generic name and be confident that drugs meeting the highest standard are supplied.
>
> At the root of this whole problem is the fact that certain drugs have achieved acceptance by their trade names in the mind of the physician who writes the prescription. That acceptance has been won through the efforts of the industry's salesmen, who are called detail men; it has been won by sustained and expensive and, why blink at the unhappy fact, sometimes misleading advertising; and, finally, that acceptance flows from the weakness of the

law which makes it possible for a few unqualified manufacturers to operate.

* * * *

It is most unfortunate that high prices in prescription drugs should result from the fact that many doctors are uneasy about prescribing by generic names. Why is this so? The answer is that it is the weakness of the law which makes for this insecurity and makes high prices inevitable for prescription drugs.

* * * *

The stricter standards for inspection imposed by this bill, and its requirement for registration, will guarantee the quality of every drug sold in the United States. The physician will know it is of adequate and acceptable quality whether it is marketed under a brand name or under a generic name.

* * * *

MR. KEFAUVER. The Senator conducted this important part of the hearings. Is it not true that the drug manufacturers spent $5,000 a year per physician to send out detail men who provide the physician with sample drugs and give him information about their own drugs, and for other selling and promotional expenses?

MR. HART. That was indicated from our record of the hearings.

MR. KEFAUVER. Is not the principal purpose of detailing to impress on the mind of the physicians a trade name and to leave the impression that if they used a drug with a trade name of a well-known manufacturer, they were perhaps getting a purer drug or a better drug or a more efficacious drug than would be so if the drug had been purchased by the generic name at a lower price?

MR. HART. The testimony indicated clearly that that was the purpose of detail men, and that was, in fact, the way they performed.

MR. KEFAUVER. *While the provision of the bill which the Senator is talking about now, relating to stricter factory inspections and control measures, may not be as effective as licensing, it will, in the first instance, be effective and give the physician adequate grounds for relying upon the soundness, purity, strength, and efficacy of any drug purchased or manufactured in this country, whether prescribed by the generic name or by the trade name. Is that correct?*

MR. HART. *I feel that is so. Certainly it is our hope.*

* * * *

Let us not churn up the water now over the dam. Let us be thankful that we have a bill before us which will give assurance to physicians

> that if they prescribe generically the sources from which the drugs will be secured will be inspected, so that standards will be met. I think this is a most important aspect of the proposed legislation which, in the excitement and emotions following the incidents with respect to thalidomide, has been overlooked.

108 CONG. REC. S17,381-82 (1962) (emphasis supplied). *See also* S. REP. NO. 1744, 87th Cong., 2d Sess. (1962); [1962] U.S. CODE CONG. & AD. NEWS 2893-94, *cited in Generix, supra*, 654 F.2d at 1118-19. Indeed, one can read the hundreds of pages of legislative history surrounding this bill and never find any support for the Government's position other than an occasional word here or there taken out of context.

It is not surprising in light of this legislative background that the position the FDA urges now is relatively new. Beginning shortly after enactment of the Act in 1938, the FDA concluded that a drug that was substantially the same as one already approved by the agency in an NDA was not a "new drug" under § 201(p) of the Act, and therefore could be marketed without prior FDA approval under § 505.[15] Accordingly,

---

[15] *Conditions for Marketing Human Prescription Drugs*, 40 Fed. Reg. 26,142, 26,143 (1975). (R. 160-75). The preamble to this proposed rule contains the only integrated history of the FDA's interpretation of the term "new drug." The Government argued in the lower court that its decision to permit marketing of drugs without NDAs was due to "war-related staff shortages." This may have been a factor, but the FDA's Annual Report covering that period does not mention it. Instead, it refers to "the revision in policy as to what constitutes a new drug" and "the effect of the

the FDA commenced the practice of issuing "not new drug" opinions:

> [B]y 1968 the Food and Drug Administration had issued several thousand letters and oral determinations to drug manufacturers stating that various types of drugs were no longer covered by the definition of new drug in section 201(p) of the act in that they had become generally recognized as safe and effective and had been used to a material extent or for a material time, and thus that they had achieved "old drug" ("not new drug") status. Under the statute, an old drug need not be the subject of an effective or approved NDA prior to marketing

40 Fed. Reg. at 26,144 (1975). No mention is made in this account of any FDA belief that product-specific factors such as inactive ingredients, bioavailability and manufacturing procedures were relevant to the decision to issue "not new drug" opinions. Indeed, since consideration of those factors would have precluded a finding that a drug was "generally recognized" as safe and effective, it follows that from shortly after passage of the Act until 1968, the FDA viewed the "new drug"

(Footnote 15 Continued)

war on the development and marketing of new-drug products." [1942-1943] FDA ANN. REP. at 47. (R. 1976-79). The Federal Register document merely confirms that the agency's practice, which continued for more than 30 years, was based on a considered judgment that a drug that was the same as one for which an NDA was already approved was not a "new drug" as a matter of legal interpretation.

definition as applying only to generic drug entities, not to specific products.[16]

It was not until 1968 that the FDA abandoned the policy of issuing "not new drug" opinion letters. 40 Fed. Reg. at 26,143. Even then, however, the FDA did not modify its interpretation of the "new drug" definition:

> [T]he agency fully realized that it would not be feasible from an administrative standpoint, or necessary for protection of the public health, or consistent with the definition of new drug in section 201(p) of the act to require either a full or an abbreviated NDA for all human prescription drugs.

40 Fed. Reg. at 26,144 (1975). At about that time, the FDA commenced the practice of approving what is

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[16]The FDA's interpretation continued well beyond the 1962 amendments. The Government has implied that the 1962 amendments prompted a change in the FDA's interpretation of the "new drug" definition. This view is belied by the cited Federal Register account and by the following excerpt from a 1963 letter from John F. Palmer, Chief of FDA's New Drug Status Branch, Division of New Drugs:

> However, new manufacturers desiring to market an article no longer regarded as a new drug would not be required to submit new drug applications, although they would, of course, have to comply with all pertinent requirements of the Act and regulations relating to adulteration and misbranding including, as an example, the "current good manufacturing practice" regulations.

Letter from John F. Palmer to Lennart Lindberg (drug company executive) (Oct. 2, 1962). (R. 180-85).

known as an "abbreviated NDA," or ANDA, to regulate drugs whose safety and effectiveness are well-established. An ANDA is an NDA that does not include safety and effectiveness data on a drug's active ingredient, but does include product-specific information, such as bioavailability and manufacturing data.

The ANDA is a regulatory hybrid whose legal validity has never been established. FDA concedes that drugs for which it requests an ANDA are "generally recognized as safe and effective":

> If one analyzes the notice [permitting the filing of an ANDA], it implies that the generic drug is generally recognized as safe and effective, and hence is not a new drug because no additional safety and effectiveness data need be submitted in the ANDA.

McEniry, *Drug Monographs*, 29 FOOD DRUG COS. L.J. 166 (1974).

Obviously, if a drug is not a "new drug," no NDA, abbreviated or otherwise, may legally be required by the FDA. In fact, the ANDA system has achieved a certain grudging toleration by the drug industry. To avoid a confrontation, most drug companies will comply with the FDA's demands regardless of their skepticism about the validity of what the agency wishes them to do. It is nevertheless a fact that the FDA's insistence on ANDAs for drugs that are not "new drugs" has no basis in law. Because the ANDA system is also cumbersome and unpredictable, and may involve lengthy delays (R. 204-05), a number of manufacturers of generic

drugs market their products without applying for ANDAs, as it is their legal right to do.

The change in the FDA's position coupled with the decisions by some manufacturers to market generic drugs without applying for (or, in some cases, awaiting approval of) ANDAs resulted in litigation. Three courts of appeal have discussed the issue involved here.[17] The Third Circuit has decided two cases. *Pharmadyne Laboratories, Inc. v. Kennedy*, 596 F.2d 568 (3d Cir. 1979); *United States v. Articles of Drug (Lannett)*, 585 F.2d 575 (3d Cir. 1978).

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[17]This Court has not discussed this issue. Its closest decisions are *Weinberger v. Hynson, Westcott and Dunning, Inc.*, 412 U.S. 609 (1973) and *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645 (1973). Both cases address the converse of this issue and hold that withdrawal of an NDA for the brand-name product operates automatically to remove marketing approval for all of the "me-too" generic copies. This Court noted in *Bentex:*

> Clearly, if FDA were required to litigate, on a case-by-case basis, the "new drug" status of each drug now marketed, the regulatory scheme of the Act would be severely undermined, if not totally destroyed.

412 U.S. at 653. Both cases centered around the active ingredients in the various products. If, as the FDA claims, the inactive ingredients can affect the safety and effectiveness of products, withdrawal of an NDA for one product should not automatically result in a withdrawal of approval for others. Moreover, these decisions would have been totally unnecessary if each generic product must be "generally recognized" as safe and effective to escape regulation. Products cannot generally be so recognized. Therefore the FDA could have proceeded against them in court as unapproved new drugs without reference to the lack of safety and effectiveness of the pioneer.

In *Lannett*, the district court granted the Government's motion for summary judgment on the ground that Lannett's drugs were "new drugs" because Lannett had failed to ask the FDA to grant a hearing on that issue. *United States v Articles of Drug (Lannett)*, [1977 Transfer Binder] FOOD DRUG COS. L.REP. (CCH) ¶38,415 (E.D.Pa.). The court of appeals reversed the decision. It held that the FDA's notices of opportunity for hearing did not clearly apprise Lannett that its drugs would be adversely affected by the agency's proposed actions. *United States v Articles of Drug (Lannett)*, 585 F.2d 575 (3d Cir. 1978).

The court of appeals went on to discuss in dicta the critical issue in this case, the application of the "new drug" definition to generic drugs. 585 F.2d at 581-84. The court described the FDA's position as follows:

> The FDA . . . maintains that for each specific drug product there must be general recognition of its safety and efficacy. This, the FDA contends is especially true if applied to the bioavailability (ability of the active ingredient of a drug to get to the bloodstream), the bioequivalence (comparison of one drug to another), and the quality control problem of specific drugs such as Lannett's.

585 F.2d at 582. Lannett argued that

> all of its drugs have been admitted by the Government as being the same generically as a drug already approved as safe and effective. Therefore, it contends that all that is required by the "new drug" section—*general* safety

> and effectiveness recognition—has been provided and that bioavailability, bioequivalence, and other quality control tests are irrelevant as to safety and efficacy.

Id. The court concluded that Lannett's interpretation of the "new drug" definition was correct. *Id.* It remanded the case to the district court for an evidentiary hearing on the "new drug" status of Lannett's products.

In *Pharmadyne Laboratories, Inc. v. Kennedy*, 466 F.Supp. 100 (D.N.J. 1979), the district court declined to follow its own court of appeal's analysis of the "new drug" definition. Instead it adopted the FDA's theory that each product must meet the "general recognition" test, or else be approved by the FDA as a "new drug." Because the plaintiff in that case sought to enjoin ongoing court enforcement actions, the district court's dismissal of the complaint was upheld on the unrelated ground that a district court may not enjoin institution of a court proceeding. *Pharmadyne Laboratories, Inc. v. Kennedy*, 596 F.2d 568 (3d Cir. 1979).[18]

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[18]The Government claims that the Third Circuit retreated from *Lannett* in *Pharmadyne*. A reading of the *Pharmadyne* opinion shows no retreat. In *Pharmadyne*, the FDA introduced evidence that the inactive, and perhaps the active, ingredients in Pharmadyne's drugs were not identical to those used in the approved drug and that the differences could create a health risk. On the basis of this evidence, the court concluded that the issue raised in *Pharmadyne* was not decided in *Lannett*. 596 F.2d at 571, n.6. Here, the Government did not introduce evidence that the products were not identical or that Generix' formulations could create a health risk.

Each Third Circuit decision contains statements which partially support the positions of the parties here. However, the statements presented are dicta, not holdings. They were based on the less than full records which had been developed at early stages in the proceedings.

The second court to discuss the issue was the Second Circuit in *Premo Pharmaceutical Laboratories, Inc. v. United States, supra.* However, the *Premo* court reached its conclusion on the basis of different records and different arguments presented by the parties. It held that a drug product must be classified as a "new drug" unless the manufacturer can show, *inter alia*, that the drug product is generally recognized among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs. The position of the Government's experts in this case was that they would never generally recognize the safety and effectiveness of a drug product unless it was approved by the FDA. The *Premo* standard generally, as applied to this case, results in a "Catch-22" construction of the statute which renders it a useless nullity. Moreover, the argument Generix presented to the Eleventh Circuit was not squarely made to the Second Circuit since Premo, as an appellee, was attempting to affirm the trial judge. It is not surprising that the Second Circuit reached a different conclusion.

Against this backdrop of court decisions, the results of which were prompted by differences in issues, evidence and argument, Congress has undertaken to reconsider the relevant portions of the Federal Food, Drug and Cosmetic Act. One of the bills presented to it was S. 1075, 96th Cong., 2d Sess. The proposed legislation

would have legitimized many of the FDA's current practices. It would have eliminated the "new drug" concept:

> S. 1075 would . . . [eliminate] the concept of "new drug" and, together with other provisions, establish a single regulatory system for all drugs marketed in the United States. The effect of this provision, together with amendments to the drug approval process, is to make all drugs, with certain narrowly defined exceptions, subject to the approval process and the concomitant regulatory controls.

S. REP. NO. 96-321, 96th Cong., 2d Sess. 14 (1979). It would have "expand[ed] the factors considered by the FDA in determining whether the methods used in . . . the manufacture of a drug are adequate by adding as new factors a drug's stability and bioavailability." *Id.* at 16. It would have allowed the FDA to use an "abbreviated approval procedure for generic versions of a drug that has been approved under the Act for at least 7 years. . . ." *Id.* It would have specifically distinguished between prescription and OTC drugs. *Id.* at 19. And it would have continued to allow the marketing of OTC drugs if they were found to be generally recognized as safe and effective and not misbranded. *Id.* Although no changes have been made in the Act to date, the legislative battle for change is not yet over.

There are sound reasons to allow the debate to continue in Congress before its reaches this Court. The Government has consistently relied on unproven allegations of health and safety problems in support of

its argument. But courts cannot summon all relevant evidence and data before they reach a conclusion. Indeed, as the decisions to date have shown, the legal issues have been decided on the basis of inconclusive and often fragmentary evidence about the issues. The record in this case, for example, does not disclose whether the inactive ingredients in the Generix drugs are the same as the inactive ingredients in the brand name drugs. Even the Second Circuit in *Premo* did not decide whether a generic drug with the same inactive ingredients as the brand name drug would require an NDA.[19]

Moreover, courts generally do not have access to the type of data which enables Congress to make the cost/benefit analysis which inheres in decisions like this. This record shows that the FDA has never heard of a problem with these particular drugs. But do problems exist with other drugs? If so, what types of problems are they? What would be the cost to the consumer of solving these problems? Does the cost outweigh the potential benefit? It would be scant consolation to an aged widow whose generic heart medicine has been taken off the market because it may not be bioequivalent to the brand name if she cannot afford to buy the brand

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[19]*See, Premo, supra*, 624 F.2d at 805, n.9.:

> Since the excipients in Insulase differ from those in Diabinese and a difference in excipients may affect the safety and effectiveness of a drug, even though the active ingredients are the same, it becomes unnecessary for us to decide whether an identical, precise copy of an FDA-approved drug, which contains the exact same ingredients and excipients in the same proportions may successfully claim general recognition based on FDA-approval of the drug product which has been copied.

name. Generix respectfully suggests that the legal issue involved here is not ripe for review by this Court. This Court should allow Congress and the lower courts more time to analyze the issue and all its ramifications. The apparent conflicts in the decisions may be resolved in further cases or mooted by Congressional action. If not, the issue will be ready for exploration by this Court.

CONCLUSION

For these reasons, the petition for a writ of certiorari should be denied.

Respectfully submitted,

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Petitioner's Reply Brief

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No. 81-1222

In the Supreme Court of the United States

OCTOBER TERM, 1981

UNITED STATES OF AMERICA, PETITIONER

v.

GENERIX DRUG CORPORATION, ET AL.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE ELEVENTH CIRCUIT

REPLY MEMORANDUM FOR THE UNITED STATES

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OCTOBER TERM, 1981

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UNITED STATES OF AMERICA, PETITIONER

v.

GENERIX DRUG CORPORATION, ET AL.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE ELEVENTH CIRCUIT

REPLY MEMORANDUM FOR THE UNITED STATES

Respondents concede (Br. in Opp. 10) that the issue presented for review in this case—whether the premarketing approval requirements of the Federal Food, Drug, and Cosmetic Act apply to generic prescription drugs—is important and that the decision below conflicts with the ruling of the Second Circuit in *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, 629 F. 2d 795 (1980). They argue, however, that certiorari should not be granted because Congress, rather than the Court, should resolve this conflict (Br. in Opp. 10, 26-27), and because the lower courts also should be given more time to "analyze the issue

and all its ramifications" (Br. in Opp. 28). Neither argument has merit.[1]

1. The possibility that Congress might decide to amend the Act does not obviate the need for this Court to resolve a conflict among the circuits over an important provision of that Act as it now stands. At least that is so when, as is true here, there is no pending legislation that would alter or clarify the statutory provisions at issue.[2] As things stand, Congress has determined that the need for premarketing review of "new drugs" outweighs the expense that such review may involve.[3]

2. Nor will additional lower court decisions resolve the conflict between the court below and the Second Circuit. As we have argued (Pet. 22), the fact that the question of the "new drug" status of generic prescription drugs has arisen in several cases and may arise with increasing frequency in the future militates in favor of review by this Court. For this Court to decline to resolve that issue would only exacerbate

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[1]We will not respond here to respondents' substantive arguments. Our views are set forth in the petition and will be amplified in further briefing if certiorari is granted. For this reason, we reply in this memorandum only to respondents' sole argument opposing the petition—that despite the conflicting court of appeals decisions on the important issue presented, this Court should await further cases and possible legislative revisions.

[2]The bill referred to by respondents (Br. in Opp. 25-26), S. 1075, 96th Cong., 1st Sess. (1979), was never passed by the House, and no similar legislation has been introduced in the 97th Congress.

[3]Respondents (Br. in Opp. 11), like the court of appeals (Pet. App. 5a), fail to suggest any ground for disregarding the plain language of 21 U.S.C. 321(g)(1)(B) on which we rely in arguing that generic drugs are "drugs" within the meaning of the Act (Pet. 9-11). Respondents (Br. in Opp. 12-18) and the court of appeals (Pet. App. 13a-14a) also misinterpret the legislative history of the 1962 amendments to the Act, which does not indicate that Congress intended to exempt generic drugs from the premarketing approval requirements of 21 U.S.C. 355 (Pet. 16-18).

the present confusion and uncertainty that the FDA, as well as drug manufacturers and distributors, now face and make it more difficult for the FDA to enforce the new drug provisions of the Act, which are essential to protect the public from potentially unsafe or ineffective drugs (see Pet. 23).

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

REX E. LEE
Solicitor General

FEBRUARY 1982

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Respondent's Reply Brief

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CASE NO. 81-1222.

in the

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of the

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OCTOBER TERM, 1981

UNITED STATES OF AMERICA,
Petitioner,

vs.

GENERIX DRUG CORPORATION, ET AL.,
Respondents.

On Petition for a Writ of Certiorari to
The United States Court of Appeals
For the Eleventh Circuit

SUGGESTION OF MOOTNESS OF RESPONDENTS

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OCTOBER TERM, 1981

UNITED STATES OF AMERICA,
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GENERIX DRUG CORPORATION, ET AL.,
Respondents.

On Petition for a Writ of Certiorari to The United States Court of Appeals For the Eleventh Circuit

---

SUGGESTION OF MOOTNESS OF RESPONDENTS

Respondents GENERIX DRUG CORP., LEWIS MICHAEL ORLOVE, GARY R. DUBIN and OFELIA PEREZ [referred to collectively as GENERIX] suggest

that this case is moot.[1] When Petitioner UNITED STATES OF AMERICA [the GOVERNMENT] filed this case in 1979, GENERIX was selling products which did not have approval from the FDA in the form of NDAs [new drug applications] or ANDAs [abbreviated new drug applications]. During the course of these proceedings, GENERIX, for reasons unrelated to the legal issues involved here, stopped selling products which did not have NDAs or ANDAs.

GENERIX stopped distributing most of these products some time ago. However, until very recently, GENERIX had an interest in certain unapproved products which had been seized by the FDA. These seizures are the subject of forfeiture actions which are separate from this injunction case. The trial court granted GENERIX' motion for summary judgment in the forfeiture cases and ordered the products returned to GENERIX. The GOVERNMENT appealed. That appeal is currently pending before the Eleventh Circuit as Case No. 81-6234. The District Court and the Eleventh Circuit denied the GOVERNMENT's motion to stay the return of the property. However, this Court granted the stay. Case No. A-617. The shelf lives of the vast majority of the seized drugs have expired. The drugs cannot be sold legally whether or not they require approval. The shelf lives of the remaining drugs are so short that the products cannot be sold. GENERIX is therefore abandoning its claim to these drugs. The Eleventh Circuit case is now moot. GENERIX has so informed the Eleventh Circuit. (App. C).

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[1]This suggestion of mootness does not reflect GENERIX' position on the merits of this case. GENERIX believes that the Eleventh Circuit's decision was correct. It intends to defend the decision if this Court finds that the case is not moot.

GENERIX informed the GOVERNMENT that it is no longer selling drugs which do not have NDAs or ANDAs. It told the GOVERNMENT that it consented to the entry of a permanent injunction preventing it from selling drugs which do not have NDAs or ANDAs in the future. (App. A).

The GOVERNMENT responded to GENERIX' letter. (App. B). It claims that it would be difficult to convince this Court to enter an injunction based on the consent of the parties. GENERIX does not know whether or not this is true, but sees no legal impediment to the procedure.

The GOVERNMENT claims that consent to an injunction is not sufficient. It believes that a recall of all unapproved products sold in the past is necessary.[2] The case is moot even if the FDA has the power to recall.[3] According to GENERIX' records, the shelf lives on the drugs it has sold have expired. The drugs cannot be sold legally by anyone whether or not they have FDA approval. The GOVERNMENT questions whether the shelf lives have in fact expired. If the GOVERNMENT wishes, it can examine GENERIX' records to satisfy itself that GENERIX' claim is correct. In the alternative,

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[2]GENERIX does not consent to a recall.

[3]It is questionable whether the FDA has the power to order a recall. *National Confectioners Ass'n v. Califano*, 590 F.2d 690, 694 (D.C. Cir. 1978); *United States v. C.E.B. Products, Inc.*, 380 F.Supp. 664, 672 (N.D.Ill. 1974) (FDA does not have power to order recall). *But see United States v. K-N Enterprises, Inc.*, 461 F.Supp. 988, 991 (N.D.Ill. 1978).

the case can be remanded to the trial court for an evidentiary hearing on this issue.

Finally, the GOVERNMENT expresses concern that unless the Eleventh Circuit's decision is reversed, "the court of appeals could adhere to its view in future litigation." If this case is moot, it should be dismissed with directions to vacate all prior proceedings in the case, including the opinions rendered by the Eleventh Circuit and District Court. *United States v Munsingwear*, 340 U.S. 36 (1950). The Eleventh Circuit's decision will have no further precedential effect.

GENERIX cannot guarantee that another court in another case may not reach the same result reached by the Eleventh Circuit here. However, this Court does "not sit to decide hypothetical issues or to give advisory opinions about issues as to which there are not adverse parties before us." *Princeton University v Schmid*, ____U.S.____, 102 S.Ct. 867, 868 (1982). Where a case is moot with respect to the parties before this Court, this Court will reach the merits only in the "exceptional situation" where the acts are "capable of repetition, yet evading review." *DeFunis v Odegaard*, 416 U.S. 312, 319 (1974). The legal issue before this Court will not evade review. It can be reviewed in any other case in which the GOVERNMENT alleges similar violations.

CONCLUSION

WHEREFORE, for the reasons stated, GENERIX suggests that this case is moot. GENERIX requests this Court to enter a permanent injunction restraining it from distributing products which do not have NDAs or ANDAs. If this Court believes that it would be appropriate for the parties to present evidence to determine whether the recall claim in the case is moot, i.e., evidence concerning whether or not the shelf lives of the unapproved drugs which have been sold are expired, GENERIX requests this Court to remand this case to the trial court for the purpose of conducting an evidentiary hearing on the issue.

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April 13, 1982

APPENDIX A

March 26, 1982

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Assistant to the Solicitor General
Department of Justice
Washington, D. C. 20530

Re: *United States v. Generix Drug Corp., et al.*
Our File No. 80-006

Dear Mr. Ganzfried:

This letter will confirm our recent conversations about this case. My clients, Generix Drug Corp., Michael Orlove, Ofelia Perez and Gary Dubin, have stopped selling drugs which do not have NDAs or ANDAs. Their decision was based on marketing considerations unrelated to the legal issue involved in this case.

In light of this decision, my clients would agree to entry of a permanent injunction preventing them from distributing unapproved drugs. They would not take any position with respect to the Fifth Circuit's decision, i.e., they would not confess error. You questioned whether they would also consent to a recall of all unapproved drugs they have sold in the past. To the best of our knowledge, all of the unapproved drugs sold in the past have shelf lives which have already expired. They cannot be sold legally by any persons now possessing them. Therefore, a recall, in addition to being almost impossible from a practical point of view, is also unnecessary.

In light of my clients' desire to consent to the relief sought, they are no longer "interested" parties in these proceedings. The case is, as far as they are concerned, moot. We intend to inform the Supreme Court of our position and to seek appropriate relief. We believe that the Court's decision in *United States v. Munsingwear, Inc.*, 340 U.S. 36 (1950) governs this type of situation. We will request the Court to enter the injunctive relief sought by the Government, dismiss the case, and vacate all prior opinions in the proceedings, including those in the Fifth Circuit and District Court.

I must also point out that we believe the Fifth Circuit's decision is correct. If the Supreme Court decides for any reason that our case is not moot, we will defend the Fifth Circuit's decision. Our position that the case is moot should not be misconstrued as any type of comment on the merits of the litigation.

Before filing our motion, I would like to know officially what the Solicitor General's opinion is. I would appreciate your prompt attention to this matter because of the stringent time deadlines under which we are operating.

Thank you for your anticipated cooperation.

Very truly yours,

/s/ Robyn Greene
Robyn Greene

RG/ss

cc: Kenneth Sawyer, Esq.

APPENDIX B

April 2, 1982

Robyn Greene, Esquire
Greene & Cooper, P.A.
Suite 500 Roberts Building
28 West Flagler Street
Miami, Florida 33130

Re: *United States v. Generix Drug Corporation, et al., No. 81-1222*

Dear Ms. Greene:

I have reviewed your letter of March 26, 1982, to Mr. Jerrold Ganzfried of this office. For several reasons, I have concluded that your proposal would neither render the case moot nor provide a satisfactory basis upon which to conclude the litigation. Without providing an exhaustive statement of the reasons for my decision, I will briefly respond to some of the points you raise.

As you know, voluntary cessation of allegedly unlawful acts has long been held not to moot a case. See, *e.g.*, *United States v. Concentrated Phosphate Export Association*, 393 U.S. 199, 203 (1968). You accordingly suggest a permanent injunction against your clients. But, in the present posture of the case, we believe that, absent a reversal of the court of appeals decision, there would be substantial difficulty in persuading the Supreme Court or the lower courts to enter even the limited injunction you propose.

At all events, we do not believe the limited injunction you suggest would dispose of the case on a suitable

basis. I am informed by the Food and Drug Administration that it has reason to question whether the shelf lives of all drugs involved in the case have expired. We are therefore reluctant to acquiesce in an injunction that fails to provide for a recall. In particular, we have a continuing concern that a potential health risk would be created by the availability of unapproved drugs, coupled with the possibility that, unless the present decision is reversed, the court of appeals could adhere to its view in future litigation.

Accordingly, we intend to adhere to the briefing schedule for presenting to the Supreme Court the important issues raised by this case.

Sincerely yours,

/s/ Rex E. Lee
Rex E. Lee
Solicitor General

APPENDIX C

IN THE UNITED STATES COURT OF APPEALS FOR THE ELEVENTH CIRCUIT

CASE NO. 81-6234

UNITED STATES OF AMERICA
Plaintiff/Appellant

vs.

UNDETERMINED QUANTITIES OF ARTICLES OF DRUGS, etc.,
Defendant/Appellee.

RESPONSE TO APPELLANT'S MOTION TO HOLD CASE IN ABEYANCE

Appellee GENERIX DRUG CORPORATION does not oppose Appellant's motion to hold case in abeyance since the shelf lives of the products which are the subject of this seizure case have expired and the case is now moot.

Respectfully submitted,

GREENE & COOPER, P.A.
500 Roberts Building
28 West Flagler Street
Miami, Florida 33130
Telephone: 371-1597

By: /s/ Robyn Greene
ROBYN GREENE

Petitioner's Reply Brief

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No. 81-1222

In the Supreme Court of the United States

OCTOBER TERM, 1981

UNITED STATES OF AMERICA, PETITIONER

v.

GENERIX DRUG CORPORATION, ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE ELEVENTH CIRCUIT

BRIEF IN RESPONSE TO MEMORANDUM FOR RESPONDENTS SUGGESTING MOOTNESS

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In the Supreme Court of the United States

OCTOBER TERM, 1981

No. 81-1222

UNITED STATES OF AMERICA, PETITIONER

v.

GENERIX DRUG CORPORATION, ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE ELEVENTH CIRCUIT

BRIEF IN RESPONSE TO MEMORANDUM FOR RESPONDENTS SUGGESTING MOOTNESS

INTRODUCTION

Prior to the commencement of this action the government had issued a series of warnings to Generix admonishing it not to sell unapproved drugs (see J.A. 11-15, 17).[1] Despite Generix's assurances that it would not violate the law in the future (J.A. 14, 38, 52), Generix continued to sell unapproved prescription drugs. This action for injunctive relief followed, as did seizure actions directed at condemning unapproved drugs in Generix's possession (see Gov't Br. 3 n.6).

[1] "J.A." refers to the joint appendix filed in this Court. "Gov't Br." refers to the government's merits brief filed on April 15, 1982. "Generix Mem." refers to the Suggestion of Mootness of Respondents.

For more than two years the issues now before this Court on writ of certiorari were hotly contested by the parties in the lower courts. In January 1982, Generix stoutly disputed the government's interpretation of the Federal Food, Drug, and Cosmetic Act (the Act) when it opposed the government's motion for a stay pending appeal from an order in the seizure cases that would have released unapproved drugs to Generix for resale. *United States* v. *Undetermined Quantities of Articles of Drugs*, stay granted by the Supreme Court, No. A-617 (Jan. 18, 1982). And, as recently as February 1982, when they filed a brief in opposition to the petition for a writ of certiorari, respondents continued to challenge the government's view. Not until three months after the stay was entered and more than one month after certiorari was granted in No. 81-1222 did Generix suggest to the Court the possibility that the case is moot. In fact, the case is not rendered moot by respondents' unilateral promise to refrain from selling unapproved drugs; their belated suggestion presents no occasion for the Court to decline to rule on the important question as issue. Indeed, respondents' memorandum reflects on its face the continuing controversy between the parties on the proper interpretation of the Act and the scope of appropriate relief. See Generix Mem. 2 n.1, 3 n.2.

To put the issue in perspective, the "burden of demonstrating mootness 'is a heavy one,' " *County of Los Angeles* v. *Davis*, 440 U.S. 625, 631 (1979), quoting *United States* v. *W.T. Grant Co.*, 345 U.S. 629, 633 (1953). Generix has not taken the first step in meeting this heavy burden. Specifically, respondents point to no legally significant change in circumstances occurring since the case was decided by the court of appeals. At best, respondents offer a promise

of voluntary cessation of illegal activities, a gesture that does not moot the case.

Respondents' remaining contentions are directed toward the possibility that some court will enter the limited injunction they now propose. But, because respondents expressly reject some of the relief the government is seeking in this proceeding (Generix Mem. 3 n.2; see *infra*, pages 5-10), the proposed injunction, even if entered, would not render the case moot. The proposal, at all events, does not provide a satisfactory basis for terminating the case. Moreover, as discussed below, we harbor serious doubts whether Generix's proposed injunction could be entered by any court unless the decision below is reversed.

Finally, important considerations of public policy counsel the conclusion that the case should be decided on the merits. Unless it is reversed, the decision below will cripple FDA's ability to protect the public from potentially unsafe and ineffective drugs as Congress intended—by keeping them off the market.

I. THE CASE IS NOT MOOT BECAUSE THE CIRCUMSTANCES EXISTING AT THE TIME OF THE DECISION BELOW HAVE NOT SIGNIFICANTLY CHANGED

A. It has long been settled that voluntary cessation of challenged conduct does not render a case moot.[2] *United States* v. *Concentrated Phosphate Ex-*

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[2] Because a determination of mootness ordinarily results in the dismissal of a case (see *United States* v. *Munsingwear*, 340 U.S. 36 (1950)), this Court has traditionally found cases not to be moot unless the entire case is resolved and there is no possibility of "any effectual relief whatever," *Mills* v. *Green*, 159 U.S. 651, 653 (1895); *Deposit Guaranty National*

port Association, 393 U.S. 199, 203 (1968). See *United States* v. *Trans-Missouri Freight Association*, 166 U.S. 290, 308-309 (1897); *Walling* v. *Helmerich & Payne*, 323 U.S. 37, 42-43 (1944); *United States* v. *W.T. Grant Co.*, *supra*, 345 U.S. at 632. In the present posture of the case, all that Generix can posit as the basis for its suggestion of mootness is its voluntary cessation.

B. Although Generix envisions that its proposal will be incorporated in a permanent injunction, no such injunction has been entered to date and we anticipate significant difficulties in doing so unless this Court reverses the decision below. As the case stands now, of course, the suggested mootness is merely prospective, in contemplation of future judicial acts, a situation that is not the equivalent of mootness.

Bank v. *Roper*, 445 U.S. 326 (1980); *United States* v. *Concentrated Phosphate Export Association*, 393 U.S. 199, 203 (1968) ("A case might become moot if subsequent events made it absolutely clear that the allegedly wrongful behavior could not reasonably be expected to recur."); *City of Mesquite* v. *Aladdin's Castle, Inc.*, No. 80-1577 (Feb. 23, 1982). Thus, a case may be moot when the moving party or a criminal defendant has died (*e.g.*, *Fletcher* v. *Bryan*, 361 U.S. 126 (1959); *List* v. *Pennsylvania*, 131 U.S. 396 (1888)); when a case has been settled (*e.g.*, *Stewart* v. *Southern Ry.*, 315 U.S. 784 (1942); *J. Aron & Co.* v. *Mississippi Shipping Co.*, 361 U.S. 115 (1959)); when an act sought to be enjoined has irretrievably occurred (*e.g.*, *Brockington* v. *Rhodes*, 396 U.S. 41 (1969); *Brownlow* v. *Schwartz*, 261 U.S. 216 (1923); cf. *SEC* v. *Medical Committee for Human Rights*, 404 U.S. 403 (1972); but cf. *Dunn* v. *Blumstein*, 405 U.S. 330 (1972)); or when the statute that is the basis for the action is repealed (*e.g.*, *Diffenderfer* v. *Central Baptist Church*, 404 U.S. 412, 414-415 (1972); *Hall* v. *Beals*, 396 U.S. 45, 48 (1969); *Amalgamated Association of Employees* v. *Wisconsin Board*, 340 U.S. 416 (1951)). None of these events of conclusive termination has occurred here.

Respondents apparently entertain the notion that this Court will enter the proposed decree, but they suggest no basis upon which this Court could do so. We regard it as highly unlikely that this Court would enjoin respondents in the absence of a ruling on the merits. This is particularly the case since the entry of an injunction would presumably vest this Court with continuing jurisdiction over the matter and require that any future proceedings for, *inter alia*, enforcement, contempt or modification, be original actions before the Supreme Court.

Moreover, absent reversal by this Court correcting the erroneous holding of the decision below, we perceive significant barriers to the entry of the proposed injunction in the lower courts. The court of appeals, in directing that the complaint be dismissed, ruled that the Act permits generic prescription drugs to be sold with no premarketing clearance whatsoever (see Gov't Br. 9-11). The district court, although it entered a partial preliminary injunction, also disagreed with the government's interpretation of the Act (see *id.* at 8). In these circumstances there remains the strong possibility that neither lower court would summarily reverse its prior holding, which entry of the proposed injunction would require, absent reversal by this Court.

II. THE CASE IS NOT MOOT BECAUSE THE PROPOSED INJUNCTION FAILS TO INCLUDE ALL FORMS OF RELIEF DEMANDED BY THE GOVERNMENT

A. The government's complaint in this case sought, *inter alia*, an injunction against the sale of unapproved drugs and a recall of such drugs Generix had already distributed. In suggesting that the Court not hear this case on the merits, Generix announces its

intention to consent to the entry of a permanent injunction on but one of the government's demands for relief. That proposal, even if it were a suitable basis for terminating the case, does not render the case moot. Generix proposes only that it be enjoined from selling drugs that do not have approved new drug application (NDAs) or abbreviated new drug applications (ANDAs); Generix does not consent to the recall that the government sought in its complaint (J.A. 21-22) and motion for preliminary injunction. The government has not acquiesced in Generix's unilateral selection of certain requests for relief and rejection of others. See *United States* v. *Ward Baking Co.*, 376 U.S. 327, 334 (1964).

Generix's express refusal to consent to the recall demanded by the government (compare Generix Mem. 3 n.2 with J.A. 21-22, 32-33) requires the case to proceed. *Deposit Guaranty National Bank* v. *Roper*, 445 U.S. 326, 333 (1980) ("[n]or does a confession of judgment by defendants on less than all the issues moot an entire case"); cf. *Electrical Fittings Corp.* v. *Thomas & Betts Co.*, 307 U.S. 241 (1939). The pendency of the recall issue is of paramount importance in light of respondents' suggestion that the entire case be dismissed as moot (Generix Mem. 4).[3]

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[3] When the district court entered a partial preliminary injunction it denied the government's request for a recall as a provisional remedy (see Gov't Br. 9 n.16; Pet. App. 30a-31a). The demand for a recall nevertheless remains in the case for disposition after trial.

Recall of violative products has often been found to be an appropriate enforcement tool under the Act. *See, e.g., Reich* v. *United States*, 239 F.2d 134, 136 (1st Cir. 1956), cert. denied, 352 U.S. 1004 (1957); *United States* v. *Medwick Laboratories, Inc.*, 416 F. Supp. 832 (N.D. Ill. 1976); *United States* v. *Lanpar Co.*, 293 F. Supp. 147, 155 (N.D. Tex. 1968); *United*

If that were to occur, the government would be prevented from obtaining relief essential to protection of the public health. Cf. *Ward Baking Co., supra*; *Deposit Guaranty National Bank, supra.*

Thus, this case is similar to *Memphis Light, Gas & Water Division* v. *Craft*, 436 U.S. 1 (1978), in which plaintiffs' demand for a hearing and certain equitable relief had become moot. Claims for actual and punitive damages, however, remained. This Court stated that the monetary claim (436 U.S. at 8-9) (citation and footnote omitted):

> saves this cause from the bar of mootness. * * * Although we express no opinion as to the validity of respondents' claim for damages, that claim is not so insubstantial or so clearly foreclosed by prior decisions that this case may not proceed.

See *Deposit Guaranty National Bank* v. *Roper, supra; Moose Lodge No. 107* v. *Irvis*, 407 U.S. 163, 170 (1972).

B. Generix also suggests, incorrectly, that the recall request itself has been mooted by the passage of time. Thus, respondents state, without any support-

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States v. *Premo Pharmaceutical Laboratories, Inc.*, No. 80-699 (D.N.J. Feb. 9, 1981) (supplemental order of preliminary injunction).

When the judicial recall authority under the Act has been questioned, the courts have split. Compare the strong affirmation of that authority in *United States* v. *K-N Enterprises, Inc.*, 461 F. Supp. 988 (N.D. Ill. 1978), with *United States* v. *Superpharm Corp.*, Cv-81-0087 (E.D.N.Y. Dec. 8, 1981); and *United States* v. *C.E.B. Products, Inc.*, 380 F. Supp. 664 (N.D. Ill. 1974). Some courts have suggested that in appropriate circumstances a recall order may be grounded on the court's general equitable authority. See *United States* v. *Spectro Foods Corp.*, 544 F.2d 1175, 1181 & n.21 (3d Cir. 1976).

ing evidence,[4] that: "According to GENERIX' records, the shelf lives on the drugs it has sold have expired" (Generix Mem. 3). This statement is incorrect. Following Generix's invitation (Generix Mem. 3) that the government examine its corporate records, FDA did so. In the course of that examination a company official swore in an affidavit that Generix has shipped quantities of unapproved new drugs as recently as February 1981 and that the expiration dates on some of those drugs will not pass until 1983 or 1984.[5] Thus, if the government is precluded from the relief it seeks in this case because the case is declared moot, the public will be subjected to potentially dangerous drugs with unexpired shelf lives for many months to come.

Even if it were true, as it is not, that the shelf lives of the drugs Generix sold have expired, that fact would not be determinative. Respondents contend that because the drugs cannot "be sold legally" after their expiration dates (Generix Mem. 3) there is no purpose to further proceedings. This misses the

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[4] In a different proceeding before this Court, *United States* v. *Undetermined Quantities of Articles of Drugs, supra*, Generix submitted an affidavit that appears to conflict with both the assertion Generix makes here and Generix's submission to the Eleventh Circuit (Generix Mem. App. 5). The sworn statement of Generix's official, Kenneth Sawyer, states with respect to drugs involved in the seizure actions that "[a]pproximately 65% have shelf lives which will expire within the next six months" (Aff. of Kenneth Sawyer, Jan. 11, 1982, filed in this Court in *United States* v. *Undetermined Quantities of Articles of Drugs, supra*).

[5] In light of these facts, the evidentiary hearing on the expiration date of the drugs that Generix suggests (Generix Mem. 3-4) is unnecessary.

point: these drugs could never "be sold legally" absent FDA approval. Generix sold them nevertheless. Moreover, respondents can provide no assurance that the drugs will not be sold to the public after their expiration dates.

C. In addition, Generix's proposal does not address an aspect of the case that directly implicates the question whether the acts complained of are "capable of repetition, yet evading review." As stated in Generix's memorandum the proposed limited injunction would run only against the named defendants (Generix Mem. 3 & App. 1). It does not address the possibility that affiliated companies or other companies that have been or could be organized by Generix's principals be similarly barred from unlawful acts.[6] For this reason, the government's prayer for injunctive relief was directed to "the defendants * * * and all of their officers, agents, servants,

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[6] We note in this regard that the matter of corporate relationships was a subject of controversy during discovery proceedings. In a deposition taken after the district court entered a preliminary injunction, respondent L. Michael Orlove testified that he was an officer of at least one drug distributor other than Generix (Dep. Tr. 8), but counsel directed Orlove not to disclose his position in the other company (*id.* at 9). Generix is itself a subsidiary of Orlove Enterprises (*id.* at 17), which also has other subsidiaries (*id.* at 8) including the drug distributing company of which Orlove is an officer (*ibid.*) and other companies Orlove refused to reveal (*id.* at 19) (the transcript of this deposition was filed in the district court on July 8, 1981). Respondents' failure to comply with Rule 28.1 of the Rules of this Court by making the requisite disclosure of corporate relationships has perpetuated the uncertainty surrounding this issue.

employees, and attorneys and any and all persons in active concert or participation with them or any of them" (J.A. 17, 28). Generix's failure to consent to an injunction as broad as that sought by the government renders its proposal inadequate and defeats its claim of mootness. *Deposit Guaranty National Bank* v. *Roper*, *supra*, 445 U.S. at 333.

III. THE IMPORTANT PUBLIC HEALTH ISSUES INVOLVED IN THIS CASE WARRANT ADJUDICATION

As discussed in our merits brief, and as further demonstrated by the briefs amicus curiae, this case presents issues of paramount importance to public health. The question whether potentially unsafe or ineffective prescription drugs may be marketed without any review by FDA poses an issue of immediacy not only to the parties, but to all patients who have purchased or who may, under the decision below, ingest such unapproved drugs.

In such circumstances, the Court has recognized that principles favoring the continued life of a controversy "may be applied in fuller measure in furtherance of the public interest * * * than if only private interests were involved." *Walling* v. *Reuter Co.*, 321 U.S. 671, 674-675 (1944). The "public interest in having the legality of the practices settled" when coupled with a possibility of recurrence "militates against a mootness conclusion." *United States* v. *W.T. Grant Co.*, *supra*, 345 U.S. at 632.

This approach is recognized as particularly appropriate where the Court's decision will operate as a guide to the public agency if it is required to take

further action in the same matter, *Walling* v. *Haile Gold Mines, inc.*, 136 F.2d 102, 105 (4th Cir. 1943), or in future similar matters. *Walling* v. *Mutual Wholesale Food & Supply Co.*, 141 F.2d 331, 334-335 (8th Cir. 1944); *Southern Pacific Terminal Co.* v. *ICC*, 219 U.S. 498 (1911); *Boise City Irrigation & Land Co.* v. *Clark*, 131 F. 415 (9th Cir. 1904).

In this respect, the present case takes on special significance because it is a case of first impression in this Court involving an issue on which the courts of appeals have differed, and it can therefore be anticipated that a decision by this Court will affect the future administration of a statutory provision in a field where Congress was specifically concerned to protect the public interest. The decision below drastically reduces the FDA's ability to fulfill its statutory mandate of protecting the public from unapproved, untested, unsafe and ineffective drugs.

This risk is not merely hypothetical. Respondents have asserted in this proceeding that they began to distribute unapproved new drugs in reliance on dicta in a Third Circuit decision, *United States* v. *Articles of Drug . . . Lannett*, 585 F.2d 575 (1978) (J.A. 49). Given this development from dicta, the impact of a square holding by the Eleventh Circuit cannot be doubted. In fact, the court of appeals' decision in this case has already provided the rationale for the entry of summary judgment in favor of Generix in the seizure cases (see Gov't Br. 3 n.6).

In our view, these considerations, taken in combination, militate against a conclusion of mootness. *United States* v. *W.T. Grant Co.*, *supra*, 345 U.S. at 632.

CONCLUSION

The instant case has not become moot, and, accordingly, the suggestion of mootness should be rejected and the case listed for argument in due course.

Respectfully submitted.

REX E. LEE
Solicitor General

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Food and Drug Administration

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Petitioner's Brief

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UNITED STATES OF AMERICA, PETITIONER

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ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE ELEVENTH CIRCUIT

BRIEF FOR THE UNITED STATES

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QUESTION PRESENTED

Whether a prescription drug product—even though potentially unsafe or ineffective—is exempt from the requirement of premarketing approval by the Food and Drug Administration merely because it contains the same active ingredient as another drug that has received FDA approval or that is generally recognized as safe and effective.*

---

*In addition to respondent Generix Drug Corporation, the defendants in the district court were Lewis Michael Orlove, Gary R. Dubin, and Ofelia Perez, all of whom were officers or employees of Generix.

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In the Supreme Court of the United States

OCTOBER TERM, 1981

No. 81-1222

UNITED STATES OF AMERICA, PETITIONER

v.

GENERIX DRUG CORPORATION, ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE ELEVENTH CIRCUIT [1]

BRIEF FOR THE UNITED STATES

OPINIONS BELOW

The opinion of the court of appeals (Pet. App. 1a-15a)[2] is reported at 654 F.2d 1114. The decision of the district court (Pet. App. 18a-31a) is reported at 498 F. Supp. 288.

JURISDICTION

The judgment of the court of appeals (Pet. App. 16a-17a) was entered on September 4, 1981. On

[1] This case was decided by Unit B of the Fifth Circuit which, on October 1, 1981, became the Eleventh Circuit.

[2] "Pet. App." refers to the Appendix to the Petition for Certiorari filed in this case. "J.A." refers to the joint appendix filed in this Court. "Tr." refers to the transcript of the hearing in the district court on the government's motion for preliminary injunction. "R." refers to the district court record as transmitted to the court of appeals.

November 24, 1981, Justice White extended the time within which to file a petition for a writ of certiorari to and including January 2, 1982. The petition was filed on December 30, 1981, and was granted on March 1, 1982 (J.A. 66). The jurisdiction of this Court rests on 28 U.S.C. 1254(1).

STATUTES INVOLVED

The relevant statutory provisions are set forth at Pet. App. 33a-44a.

STATEMENT

1. Section 505(a) of the Federal Food, Drug, and Cosmetic Act ("the Act"), 21 U.S.C. 355(a), prohibits any person from introducing into interstate commerce any "new drug" that has not been approved by the Food and Drug Administration ("FDA").[3] The term "new drug" is defined in Section 201(p) of the Act, 21 U.S.C. 321(p), as any drug that "is not generally recognized, among experts quali-

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[3] The authority to approve new drugs, granted by statute to the Secretary of Health and Human Services, has been delegated to the Commissioner of Food and Drugs. 21 C.F.R. 5.1(a)(1); see 46 Fed. Reg. 26052 (1981). The introduction or delivery for introduction into interstate commerce of a new drug for which no approved new drug application is in effect is prohibited under 21 U.S.C. 331(d). Violations of 21 U.S.C. 331 may be enjoined under 21 U.S.C. 332. Persons who violate Section 331 are also subject to criminal penalties (21 U.S.C. 333), and drugs that fail to comply with 21 U.S.C. 355 may be seized and condemned (21 U.S.C. 334). In any of these proceedings, the actual safety or effectiveness of the unapproved drug is not an issue for the court and will not provide a defense. See *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 612-613 (1973); *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, 629 F.2d 795, 803 (2d Cir. 1980).

fied by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof,"[4] or that has not been used to a material extent and for a material time under other than experimental conditions.[5]

Generix Drug Corporation ("Generix") is a distributor of generic drugs, *i.e.*, drugs that purport to be copies of brand name or "pioneer" drugs manufactured by other companies. While the "active" ingredients of these generic drugs purport to be identical to those contained in the pioneer drugs, the "inactive" ingredients (*e.g.*, coatings, binders) may differ. Many of the generic drugs Generix sold in interstate commerce had not been approved by the FDA and, in the government's view, were "new drugs" within the meaning of the Act. After a series of warnings, respondents continued to distribute a variety of unapproved prescription drugs (J.A. 11-15, 17). Accordingly, on November 29, 1979, the United States filed an action in the United States District Court for the Southern District of Florida against Generix and several of its officers and employees. The complaint requested both preliminary and permanent injunctive relief.[6]

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[4] A drug can be "generally recognized" within the meaning of the Act only when there is an expert consensus founded upon the type of evidence necessary for approval of a new drug application (see page 22, *infra*). *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, *supra*, 412 U.S. at 632.

[5] A drug also may be excluded from the new drug approval requirements if it comes within one of the grandfather provisions of 21 U.S.C. 321(p), not relevant here.

[6] The unapproved new drugs distributed by respondents included "Goldline" products containing the following active in-

Generix did not deny that the particular drug products referred to in the complaint had not been approved by FDA.[7] The hearing on the government's request for a preliminary injunction focused, therefore, on the question whether the generic drugs distributed by Generix were "new drugs" within the meaning of 21 U.S.C. 321(p). In arguing that they were not, Generix relied on the fact that FDA had

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gredients: allopurinol, spironolactone, spironolactone with hydrochlorothiazide, furosemide, chlorothiazide with reserpine, amitriptyline with perphenazine, diethylpropion hydrochloride, prochlorperazine maleate, and chlorthalidone (R. 28 n.3). The request for injunctive relief to prevent distribution of unapproved new drugs, however, was not limited to these particular drugs (*ibid.*).

The complaint also alleged (J.A. 8-11, 15-17) that respondents were violating the Act by holding for sale and distributing in interstate commerce drugs that were adulterated within the meaning of 21 U.S.C. 351(a)(2)(B) because of failure to conform to current good manufacturing practices as set forth in 21 C.F.R. Part 211. Those allegations were not directly related to the "new drug" allegations and were resolved without trial. Thus there is no issue before this Court concerning the good manufacturing practices allegations.

In separate proceedings, commenced on August 15 and 19, 1980, the United States brought seizure actions pursuant to 21 U.S.C. 334, to condemn more than five million dosage units of unapproved generic prescription drugs in Generix's possession. Although Generix moved (without opposition) to consolidate the seizure actions with the instant injunction action, the district court did not consolidate the cases. Following the decision by the court of appeals in the injunction action, the district court granted Generix's motion for summary judgment in the seizure actions and ordered the United States to return the seized drugs. On January 18, 1982, this Court stayed the district court's order pending appeal. *United States* v. *Undetermined Quantities of Articles of Drugs*, No. A-617.

[7] R. 79-81; see also R. 28 n.3.

approved other drug products containing the same active ingredients as Generix's drugs. Such prior FDA approval, Generix argued, was evidence that the active ingredients were generally recognized as safe and effective. From this premise, Generix asserted that its products were not "new drugs" even if their inactive ingredients and methods of compounding were not identical to those used in the products previously approved by FDA.[8] Accordingly, Generix contended that the prescription drugs it distributed were subject to no FDA clearance whatever.

The government argued that FDA's prior approval of prescription drugs containing the same active ingredients as the drugs marketed by Generix was irrelevant because the Act requires FDA approval of every drug product unless that product is generally recognized as safe and effective and has been used to a material extent and for a material time. The government's evidence established that Generix's unapproved drug products were not generally recognized by qualified experts as safe and effective (Tr. 49-52, 93-94, 96-97).

In addition, the government presented evidence showing why distribution of unapproved generic drugs poses a danger to the public health. As expert witnesses explained, prescription drugs generally contain one or more active ingredients, which may comprise 10% or less of the total compound. They also contain inactive ingredients, known as excipients, whose purposes are to coat or bind the active ingredients into a convenient form and to control their solubility (Tr. 83-84). Because of differences in inactive ingredients or in methods of compounding, drugs

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[8] R. 106-149, 197-207, 212-224; Tr. 26-27, 250-253.

containing the same active ingredients can differ from each other in the amounts of the active ingredient that enter the bloodstream and the rate at which this occurs.[9] Since the quantity and speed of delivery of

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[9] The quantity and delivery speed of active ingredients to the bloodstream and thus to the site of action in the body is referred to as "bioavailability" (Tr. 39-42; see also 21 C.F.R. 320.1(a)). Drugs with similar bioavailability are considered "bioequivalent." Because differences in bioavailability can be caused by differences in either active or inactive ingredients, or by differences in methods of manufacture, drugs containing the same active ingredient may not be bioequivalent. One of the government's expert witnesses testified as follows about common causes of lack of bioequivalence (Tr. 83-84):

> The primary reason for this is that the solubility of the drug is altered, either [*sic*] because of the chemical nature of the drug, itself, which may be modified. For example, different kinds of crystalline forms dissolve in different ways. You can also alter the way that the drug dissolves by the excipients. For example, some excipients were added to the tablet to help the tableting process, a lubricant to help the tablet come out easier, are insoluble and can coat the product, itself, act as a raincoat, so the water can't get to the particles and doesn't dissolve.
>
> All drugs must dissolve in the gastrointestinal tract before they are absorbed through the membrane. So anything that alters the rate of solubility, that is the dissolution rate, may influence whether the drug is absorbed.
>
> Probably 90, 95 percent of the cases of inequivalence is because of the excipients or the way the drug is manufactured, altering the solubility.
>
> The way that the drug is manufactured also includes things such as how hard you press down on the tablet to form the tablet. Its been shown in scientific studies that simply the force of the tableting may alter the dissolution characteristics of that particle or that tablet. The tablet must first break apart in small particles. That's altered by both the ingredients and the processes of the manufacturer. Then, these small particles must break down into

active ingredients are critical factors that determine the effect of a drug on the patient, it cannot be assumed that a copy of an approved new drug will achieve the same therapeutic effect as the pioneer product (Tr. 39-40, 46-67). Often it does not.[10]

The unapproved drugs distributed by Generix include drugs prescribed for the treatment of serious and potentially life-threatening conditions such as high blood pressure (Tr. 47-48). The government's experts demonstrated that differences in formulation could affect the safety or effectiveness of such drugs (Tr. 94-98). Moreover, because the labeling of these generic products is virtually identical to that of the brand name products they copy, and because Generix markets these unapproved drugs in a way that would lead physicians to believe that they are interchangeable with approved drugs (Tr. 45-47), they create serious dangers to patients.[11]

Finally, the evidence showed that doctors and pharmacologists generally regard premarketing testing and approval as necessary to insure the safety and effectiveness of drugs. Because of the serious dangers

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further tiny particles which then go into solution. And all of these manufacturing variables influence this sequence of steps.

[10] See also *United States* v. *Premo Pharmaceutical Laboratories, Inc.*, 511 F. Supp. 958, 962-965, 980-989 (D.N.J. 1981), in which the district court made detailed factual findings on the dangers created by differences between an approved prescription drug and generic copies of that drug.

[11] For example, if the products used to treat high blood pressure do not perform properly, the patient is in serious danger either from recurrence of the high blood pressure, if absorption of the drug is inadequate, or from toxicity if the drug is overabsorbed (Tr. 47-49).

that may be created by differences in bioavailability, physicians would not knowingly prescribe an unapproved generic drug (Tr. 55-57).[12] Their willingness to prescribe generic drugs at all is based on their assumption that generic drugs have received FDA approval.

2. On June 12, 1980, the district court issued an order granting in part and denying in part the government's motion for a preliminary injunction (Pet. App. 18a-31a). Rejecting both the government's and Generix's interpretations of the Act, the court held that the government had the burden of showing a potential hazard associated with Generix's drugs.[13] The court then found that the government had presented evidence that differences in bioavailability could affect the safety and effectiveness of drugs containing any one of six active ingredients or combinations of ingredients[14] and enjoined distribution of those drugs. Because such specific evidence was not presented as to Generix's other unapproved generic drugs,[15] however, the court denied the government's motion for a preliminary injunction against distribu-

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[12] See *United States* v. *Premo Pharmaceutical Laboratories, Inc.*, *supra*, 511 F. Supp. at 963; *Pharmadyne Laboratories, Inc.* v. *Kennedy*, 466 F. Supp. 100, 106 (D.N.J.), aff'd on other grounds, 596 F.2d 568 (3d Cir. 1979).

[13] In so doing, it relied primarily on the district court decision in *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, 475 F. Supp. 52 (S.D.N.Y. 1979); that decision was subsequently reversed by the Second Circuit (629 F.2d 795 (1980)).

[14] Allopurinol, spironolactone, furosemide, chlorothiazide with reserpine, amitriptyline, and diethylpropion hydrochloride (Pet. App. 20a).

[15] Those drugs contained prochlorperazine maleate and chlorthalidone (Pet. App. 20a).

tion of those other products (*id.* at 31a).[16] The preliminary injunction was stayed pending Generix's appeal (*id.* at 32a).

3. The court of appeals reversed that portion of the district court's order granting a preliminary injunction and remanded the case to the district court with instructions to dismiss the complaint.

The court of appeals held that the term "new drug" applies only to active ingredients and not drug products. Therefore, the court concluded, a generic drug product containing the same active ingredient as an approved pioneer drug[17] is not a "new drug" and need not comply with the Act's requirement that all new drugs be approved by FDA before they are marketed. The court expressly declined to follow the recent decision in *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, 629 F.2d 795 (1980), in which the Second Circuit held that the Act's new drug definition applies to drug products, not to active ingredients alone, and that FDA approval of a brand name drug does not exempt other new drugs that contain the same active ingredient from the requirement of premarketing approval.

The court of appeals acknowledged that there may be differences in therapeutic effect between a pioneer drug product that has been approved by FDA, and

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[16] The government's request for an injunction with respect to the good manufacturing practice violations was held in abeyance pursuant to agreement of the parties (Tr. 186-187). The district court also denied the government's request for a recall of Generix's unapproved products (Pet. App. 30a-31a).

[17] The court of appeals apparently assumed that FDA approval of a drug product means that the product's active ingredient is generally recognized as safe and effective. This is incorrect. See pages 24-25, *infra*.

unapproved generic drugs having the same active ingredient but different inactive ingredients (Pet. App. 3a). It also noted the evidence that these differences "may effect [*sic*] the safety and efficacy of the generic drug product" (*ibid.*). But the court of appeals construed the Act not to protect the public from these dangers. The court concluded: "the term 'new drug' as used in [21 U.S.C.] § 321(p) applies only to the active ingredient of a drug product" (*id.* at 15a). The bases for this conclusion were the court's assumptions that "the drugs listed in the sources described in subsection (A) of [21 U.S.C.] § 321(g)(1) are 'drug substances' not drug products" and that "[i]f 'new drug' refers to the drug product as opposed to the active ingredient, a drug could never 'muster the requisite scientifically reliable evidence of effectiveness' in order to 'drop out of active regulation by ceasing to be a new drug' " as is contemplated by the Act (*id.* at 5a, 7a).[18]

The court of appeals considered the new drug approval procedures of 21 U.S.C. 355 unnecessary in the case of generic drugs because, in the court's view, the Act gave the FDA other means to regulate bioavailability and bioequivalence. The court, in addition, concluded that premarketing review of generic drugs by FDA would be contrary to Congressional intent "to encourage generic-name prescribing and thereby lower prices" (Pet. App. 10a).

Because the court of appeals concluded that in no circumstances is prior FDA approval required for a

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[18] The court also thought (Pet. App. 10a-12a) that the requirement of Section 502(e) of the Act, 21 U.S.C. 352(e), that drugs be identified by generic name in addition to brand name would be inconsistent with the inclusion of the entire drug product, rather than just the active ingredient, in the definition of "drug."

drug containing the same active ingredient as a previously approved new drug, it vacated the preliminary injunction—even as to those drugs for which there was evidence that lack of bioequivalence could be dangerous to the patient—and ordered the complaint dismissed (Pet. App. 15a).

SUMMARY OF ARGUMENT

The court of appeals' opinion ignored the plain meaning of the Federal Food, Drug, and Cosmetic Act and, consequently, reached a result at odds with clear Congressional intent and sound public policy. As a result, the court of appeals has sanctioned the distribution of unapproved—and, as far as the record reveals, untested—prescription drugs. Unless the decision below is reversed, its inevitable result will be the ingestion of such unapproved drugs by patients suffering from life-threatening ailments, patients who are in need of the assurances of safety and effectiveness the Act mandates.

The Federal Food, Drug, and Cosmetic Act prohibits the marketing of any "new drug" without prior FDA approval. 21 U.S.C. 355(a). A new drug is *any drug* that is not generally recognized by experts as safe and effective or that has not been used to a material extent and for a material time. 21 U.S.C. 321(p). The statutory language expressly provides that a generic drug product is a drug and that the Act's prohibition on marketing of unapproved new drugs applies to generic drug products. That construction of the Act is supported by the Act's legislative history and is necessary to effectuate the Act's underlying purpose—protection of the public health.

1. The Act defines "drug" to include "articles intended for use in the diagnosis, cure, mitigation,

treatment, or prevention of disease in man or other animals." 21 U.S.C. 321(g)(1)(B). Generic drug products clearly fit within this definition. Since generic drug products are drugs, 21 U.S.C. 355 prohibits the marketing of any generic drug product without FDA approval unless "such drug," *i.e.*, the generic product itself, is "generally recognized, among experts * * * as safe and effective" and has "been used to a material extent" and "for a material time." 21 U.S.C. 321(p)(1), (2). The product-specific statutory requirements for new drug applications (21 U.S.C. 355(b)) further support the conclusion that general recognition of a pioneer drug does not exempt other products containing the same active ingredient from the requirement of premarketing approval. Since evidence about the safety and effectiveness of a pioneer drug product would not be sufficient for approval of a new drug application for a generic copy of the pioneer product, such evidence is not a sufficient basis for an expert consensus that a generic copy is safe and effective. *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 632 (1973).

2. The legislative history of the new drug provisions of the Act confirms that each drug product that has not itself achieved general recognition among experts must be approved by FDA before it is marketed. The direct stimulus for the enactment of premarketing approval requirements in 1938 was the fact that numerous deaths had been caused by a new product that, although it contained an active ingredient previously used in other products, was rendered toxic by the use of an untested inactive ingredient. The 1962 amendments were intended to strengthen the protection afforded the public from potentially unsafe or ineffective drugs, and nothing in those amendments

exempts generic drug products from premarketing approval.

3. Premarketing approval of generic drug products is necessary to effectuate the Act's fundamental purpose—protection of the public health. Unapproved generic drugs may be unsafe or ineffective, and measures available to remove them from the market after they have caused harm simply do not provide the protection Congress intended. Moreover, a requirement of premarketing approval will not hamper competition in the drug industry. To the contrary, competition will be promoted by assuring that all prescription drugs on the market have satisfied the statutory standards of safety and efficacy. In the absence of the assurance provided by premarketing approval, careful doctors and pharmacists would be deterred from prescribing or dispensing generic drug products, despite lower prices.

ARGUMENT

I. THE EXPLICIT LANGUAGE OF THE ACT ESTABLISHES THAT THE ACT'S "NEW DRUG" PROVISIONS APPLY TO GENERIC DRUG PRODUCTS

This case presents a narrow question of statutory construction with broad consequences for the public health and the future of competition in the distribution of safe and effective prescription drugs. Since it is undisputed that respondents distributed generic prescription drugs without FDA premarketing approval, the issue before this Court is whether such drugs are exempt from the statutory preclearance scheme. Respondents' primary contention is that their products are not "new drugs" within the meaning of the Act. In support of this position, respondents have at various stages of this litigation relied on two prin-

cipal arguments. First, they assert that their drugs are not "new drugs" because they contain the same active ingredients as other drugs that have received FDA approval, even though the inactive ingredients may differ. Thus, it is respondents' position that their drugs should be *presumed* to be safe and effective and, consequently, exempt from FDA review, even if a difference in ingredients results in dissimilar effects on the human body. Second, respondents contend that the active ingredients in the pioneer drugs their products purport to copy have received general expert recognition as safe and effective and have been used to a material extent and for a material time, and that therefore the purported copies are not "new drugs," even though, again, the copies may contain different inactive ingredients, may have dissimilar effects on the human body, have themselves received no expert recognition, and have not been used to a material extent and for a material time.[19]

Respondents' positions fly in the face of the clear statutory language.[20] Accordingly, we turn first to

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[19] See Br. in Opp. 5 n.7. The absurdity of respondents' position is graphically illustrated by the affidavit of an expert witness submitted by Generix in opposition to the government's motion for preliminary injunction. J.A. 56-65. After noting that "all of these characteristics [inactive ingredients, manufacturing techniques, bioavailability and bioequivalence] can affect how a drug product performs and can therefore be said to play a role in the safety and effectiveness of the drug" (*id.* at 64), the affidavit concluded (*ibid.*):

> In other words, it would be possible to formulate allopurinol in a product in such a way that the allopurinol would never be released. Under those circumstances, the product would be completely ineffective, but the drug—allopurinol—would still be regarded as effective.

[20] The most important evidence of a statute's meaning is the statutory language itself. *International Brotherhood of Team-*

the express language of the Act to demonstrate that the prescription drugs at issue were, in the absence of premarketing approval, distributed unlawfully, as the Second Circuit held in *Premo Pharmaceutical Laboratories, Inc.* v. *United States, supra.*[21]

A. The Statutory Definitions of the Terms "Drug" and "New Drug" Encompass Generic Drug Products

Section 505(a) of the Act, 21 U.S.C. 355(a), prohibits the marketing of "any new drug, unless an approval of an application filed pursuant to [21 U.S.C. 355(b)] is effective with respect to such drug." The

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sters v. *Daniel*, 439 U.S. 551, 558 (1979). "Absent a clearly expressed legislative intention to the contrary, that language must ordinarily be regarded as conclusive." *Consumer Product Safety Commission* v. *GTE Sylvania*, 447 U.S. 102, 108 (1980).

[21] Other courts have reached the same conclusion as did the Second Circuit in *Premo*. For example, in *Pharmadyne Laboratories, Inc.* v. *Kennedy*, 466 F. Supp. 100 (D.N.J.), aff'd on other grounds, 596 F.2d 568 (3d Cir. 1979), the court agreed with the FDA that the "new drug" term applies to specific drug products, rejecting dicta in an earlier Third Circuit decision, *United States* v. *Articles of Drug . . . Lannett*, 585 F.2d 575 (1978), which had suggested that some or all generic copies of FDA-approved drugs do not themselves have to undergo FDA premarketing clearance. (The Third Circuit in *Pharmadyne* did not address the generic drug issue, affirming the district court instead on the ground that a court is without power to enjoin the FDA from bringing enforcement actions; but it suggested that differences in inactive ingredients, at least where those differences raise safety issues, would prohibit a generic copy from relying on the not new drug status of the pioneer it copied. See 596 F.2d at 571 n.6.) In two other actions, the FDA has obtained injunctive relief against major manufacturers of unapproved prescription drugs. *United States* v. *Pharmadyne Laboratories, Inc.*, No. 80-1312 (D.N.J., filed May 8, 1980) (consent decree of permanent injunction); *United States* v. *Premo Pharmaceutical Laboratories, Inc., supra.*

Act defines a "new drug," *i.e.*, a drug that cannot be marketed without prior FDA approval, as: "*Any drug* * * * the composition of which is such that *such drug* is not generally recognized, among experts * * * as safe and effective" or "[*a*]*ny drug* * * * which has not * * * been used to a material extent or for a material time." 21 U.S.C. 321(p)(1), (2) (emphasis added).

1. The term "drug," as used in the definition of "new drug," is broadly defined in the Act (21 U.S.C. 321(g)(1)) to include:

> (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C) of this paragraph; but does not include devices or their components, parts, or accessories.

Generic drug products are within the literal language of at least one of four subsections of this statutory definition, which this Court has held must be interpreted to provide coverage "as broad as its literal language indicates." *United States* v. *An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 798 (1969). As the Second Circuit held in *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, *supra*, generic drug products are "drugs" because they are "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." 21 U.S.C. 321(g)(1)(B).

In holding that only active ingredients and not drug products are drugs, the court of appeals in this case ignored the literal language of the statutory definition, disregarding 21 U.S.C. 321(g)(1)(B). Indeed, the court entirely omitted subsection (B) of 21 U.S.C. 321(g)(1) from its discussion, and failed to explain why it thought that a generic drug product would not fit within this definition. Rather, the court considered only another subsection of the definition of "drug" (Pet. App. 5a), 21 U.S.C. 321(g)(1)(A), and even that subsection does not support its conclusion. Thus, the court stated that the "record shows that the drugs listed in the sources described in subsection (A) * * * are 'drug substances,' not drug products" (Pet. App. 5a); but there is nothing to that effect in the record. On the contrary, the pharmacopoeia mentioned in 21 U.S.C. 321(g)(1)(A) contain monographs for drug products as well as active ingredients.[22]

More importantly, however, an article need fall within only one of the subsections of 21 U.S.C. 321(g)(1) in order to be a "drug."[23] Therefore,

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[22] For example, the most recent edition of the combined United States Pharmacopoeia-National Formulary has monographs not only for furosemide as an active ingredient but also for "furosemide injection" and "furosemide tablets." *The Pharmacopoeia of the United States of America, Twentieth Revision/The National Formulary, Fifteenth Edition* 344-345 (1980). A monograph may exist both for an "official substance," defined as "an active drug entity or a pharmaceutical ingredient * * *," and for a "dosage form," defined as the "finished * * * preparation or product of one or more official substances formulated for use on or for the patient." *Id.* at 2.

[23] No inconsistency is created by the fact that active ingredients are also "drugs." Indeed, 21 U.S.C. 321(g)(1)(D) expressly includes within the "drug" definition "articles intended

regardless of the scope of 21 U.S.C. 321(g)(1)(A), generic drug products are drugs as defined in 21 U.S.C. 321(g)(1)(B).[24]

2. Since a generic drug product is a drug, the language of 21 U.S.C. 321(p) compels the conclusion that a generic drug product is a "new drug" if *"such drug," i.e.*, the generic drug product, is not generally recognized by experts as safe and effective or has not been used to a material extent and for a material time. There is nothing in the statutory language to support the court of appeals' conclusion that a generic drug product can escape "new drug" status by virtue of general recognition of the safety and effectiveness

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for use as a component of any article [referred to in the preceding] clauses." The term "component" refers to active as well as inactive ingredients of a drug (cf. 21 U.S.C. 355(b)(2)). Therefore, a reading of Section 321(g)(1) as a whole shows that the term "drug" as defined in subsections (A), (B), and (C) must refer to drug products and not just active ingredients.

[24] The definition of "drug" in the 1906 Federal Food and Drug Act—the predecessor to the Federal Food, Drug, and Cosmetic Act of 1938—also included both drug substances and drug products. Thus, the 1906 definition of "drug" included, "*all medicines and preparations* recognized in the United States Pharmacopoeia or National Formulary for internal or external use, and *any substance or mixture of substances* intended to be used for the cure, mitigation, or prevention of disease of either man or other animals." Ch. 3915, Section 6, 34 Stat. 769 (emphasis added).

This definition was changed to the language contained in Section 321(g) when Congress enacted the 1938 Act. The purpose of that change was to *expand* and not to restrict the definition of the term "drug." See S. Rep. No. 646, 74th Cong., 1st Sess. 1 (1935) ("This expansion of the definition of the term 'drug' and the inclusion of devices are essential if the consumer is to be protected against a multiplicity of abuses not subject to the present law").

of a pioneer drug product containing the same active ingredient or of the active ingredient itself.

B. The Act's New Drug Approval Provisions Require That FDA Review New Drug Products

The conclusion that a generic drug product cannot escape "new drug" status unless the generic product is itself recognized by experts as safe and effective and has been used to a material extent and for a material time is further supported by the need to harmonize the definition of "new drug" with the Act's requirements for obtaining approval of a new drug application ("NDA"). 21 U.S.C. 355(b)-(e). See *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, *supra*, 412 U.S. at 631-632.

1. The statutory provisions governing NDAs (21 U.S.C. 355(b)) show that the FDA's premarketing review of a "new drug" is a review of the safety and effectiveness of a drug product, *i.e.*, of the combined effect of specific active and inactive ingredients. The Act requires the applicant to submit information about the components, the methods of manufacturing, and the labeling of the drug product for which approval is sought.[25] As the record in this case demon-

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[25] 21 U.S.C. 355(b) requires that an NDA contain (emphasis added):

> (1) full reports of investigations which have been made to show whether or not *such drug* is safe for use and whether such drug is effective in use; (2) a full list of the articles used as components of *such drug;* (3) a full statement of the composition of *such drug;* (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of *such drug*; (5) such samples of *such drug* and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for *such drug.*

strates, this information will be different for each new drug product, even if it has the same active ingredient as a previously approved drug product. Thus, one of the government's expert witnesses testified in this case that (Tr. 102-103):

> When you say it's "safe and effective," that depends entirely upon the drug delivery system you put it in. It's not safe if you give it in the wrong dose. Until you define the drug delivery system * * * you're dealing with, one can't say that allopurinol is safe and effective in the absence of the drug delivery system. You can say that allopurinal is a pharmacologically active drug which, in the proper use and circumstances, it can be safe and effective, but until you define those characteristics in a situation in which it is going to be used, then the terms are meaningless in my opinion.
>
> * * * * *
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> You can't say that something's safe and effective, again, a drug substance, until you define how you are going to deliver it to the body. Is it safe and effective, given intravenously? * * * Is it safe and effective by a drug delivery system that isn't absorbed? Until you define the total performance of a product, you can't make judgments on safety and efficacy of the way it will be used in humans.

In enacting the statutory approval process, Congress provided for consideration of these factors. Thus, on the basis of the information included in the application, the FDA must determine whether "adequate tests by all methods reasonably applicable" show that "such drug," *i.e.*, the drug product described in the application, "is safe for use under the conditions prescribed, recommended, or suggested in the pro-

posed labeling thereof" and whether "there is * * * substantial evidence[26] that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. 355(d).[27] Since inactive ingredients and methods of compounding can affect the safety and effectiveness of a drug product, FDA's determination that the requisite evidence of safety and effectiveness has been presented for a particular drug product cannot be viewed as a determination as to other products containing the same active ingredient. This obvious conclusion is supported by the testimony in this case, which reveals that 90-95% of those generic drugs that are not bioequivalent to the pioneers lack bioequivalence precisely because of their inactive ingredients or methods of manufacture (Tr. 83-84).

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[26] 21 U.S.C. 355(d) defines "substantial evidence" as

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is respresented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

[27] If the manufacturer wishes to make any change in the composition or labeling of the approved drug, it must first submit a supplement or amendment to the NDA. See 21 C.F.R. 314.8. If another manufacturer is licensed to produce the same drug, it too must obtain an NDA. If evidence subsequently shows that an approved drug is unsafe or ineffective or that the applicant has failed to maintain required records or to correct misleading labeling, the FDA, after opportunity for hearing, may revoke approval of the NDA. 21 U.S.C. 355(e).

As this Court has recognized, therefore, each NDA is applicable only to a specific drug product. *USV Pharmaceutical Corp.* v. *Weinberger*, 412 U.S. 655, 664 (1973). Accordingly, approval of a pioneer drug product does not permit the marketing of an unapproved generic drug containing the same active ingredient.

2. The exclusion from the "new drug" definition of drugs that are generally recognized by experts as safe and effective and have been used to a material extent and for a material time cannot be construed "to deprive FDA of jurisdiction over a drug which, if subject to FDA regulation, could not be marketed" because of the absence of sufficient evidence of its safety or effectiveness. *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, *supra*, 412 U.S. at 631. Such a construction of the statute would erroneously "impute to Congress a purpose to paralyze with one hand what it sought to promote with the other." *Ibid.* Therefore, a drug cannot be generally recognized as safe and effective unless there is an "expert consensus" that it is safe and effective and that consensus is based on tests showing safety and effectiveness that would be sufficient to warrant approval of an NDA for that product and that are available to experts in the scientific literature. 412 U.S. at 629-634; *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 652 (1973).[28]

Under the Act, however, evidence of the safety and effectiveness of a *pioneer* drug product would not be

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[28] Even if a drug satisfies the general recognition criteria, it remains a "new drug"—and requires FDA approval—unless it has been used to a material extent and for a material time under other than experimental conditions. 21 U.S.C. 321(p)(2).

sufficient to warrant approval of a generic drug containing the same active ingredient (see pages 19-22, *supra*). Therefore, even if the required expert consensus and supporting evidence in the scientific literature exist for a pioneer drug product, those facts do not provide a sufficient basis for a finding that a generic drug with the same active ingredient is not a "new drug."[29] Expert consensus supported by published evidence about the generic product itself is required.

In this case it was not disputed that there are no published studies from which experts could have reached a consensus that respondents' generic pre-

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[29] This conclusion is fully consistent with this Court's holding in *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, *supra*, that where there was no substantial evidence showing the effectiveness of a pioneer drug or of a generic copy of that drug, the FDA could conclude that both were new drugs. For if there are no adequate effectiveness tests of the pioneer drug, and the manufacturer of the generic product does not produce adequate effectiveness studies in response to a notice of opportunity for hearing, there can be no claim that the generic product has been shown by adequate testing to be effective. On the other hand, because a generic product may differ from the pioneer in bioavailability, the fact that there has been adequate testing to show the *pioneer* is safe and effective does not, in itself, demonstrate the generic product is either safe or effective. See *Pharmadyne Laboratories, Inc.* v. *Kennedy*, *supra*, 466 F. Supp. at 104 n.7; see also *United States* v. *Premo Pharmaceutical Laboratories, Inc.*, *supra*, 511 F. Supp. at 968 n.6a.

Generix is incorrect in its assertion (Br. in Opp. 22 n.17) that if the "new drug" definition applied to products, the Court's ruling in *Hynson* would have been unnecessary. At issue in *Hynson* was FDA's procedure of, in effect, declaring classes of drug products, *i.e.*, all generic copies related to a specific pioneer, to be "new drugs," thus avoiding case-by-case litigation of the status of each product. Cf. *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, *supra*, 412 U.S. at 653.

scription drugs were safe and effective.[30] Therefore, these products are "new drugs" under the plain language of the Act, and it is a violation of the Act to market them without prior FDA approval.

3. The court of appeals incorrectly assumed that FDA approval of a pioneer drug is equivalent to an agency finding that the *active ingredient* of that pioneer drug is "generally recognized" as safe and effective. In deciding whether to approve a drug product, FDA does not—and indeed could not—focus solely on the safety and effectiveness of the active ingredient. Rather, as required by the Act, it evaluates the drug product as a whole, including its inactive ingredients and methods of manufacture. 21 U.S.C. 355(b). See pages 19-21, *supra*.

Moreover, FDA's approval of a new drug application is *not* a finding that the drug is generally recognized as safe and effective, and FDA approval does

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[30] Generix's witness did not rebut government testimony to that effect (see Tr. 49, 51-52, 92-93, 96-97). Indeed, while Generix's expert witness agreed that generic drugs should not be marketed without testing (Tr. 224-225), he admitted that he had seen a test of only one of the products at issue (Tr. 219), and no evidence of *any* testing of Generix's drugs was introduced below. The unapproved drugs Generix was distributing included products manufactured by Premo Pharmaceutical Laboratories, Inc., and Pharmadyne Laboratories, Inc. (see *United States* v. *Undetermined Quantities of Articles of Drugs*, stay granted by this Court, No. A-617 (Jan. 18, 1982)), companies that subsequently have been enjoined from the manufacture of such products, see page 15 note 21, *supra*. The court that granted injunctive relief against Premo found specifically that that company placed each of its products on the market without completing testing that might determine whether or not the products were bioequivalent to those drugs for which they would be substituted. *United States* v. *Premo Pharmaceutical Laboratories, Inc.*, *supra*, 511 F. Supp. at 990-991.

not mean that the approved drug is no longer a new drug. This Court has held that:

> the Act is designed so that drugs on the market, unless exempt, will have mustered the prerequisite scientifically reliable evidence of effectiveness *long before* they are in a position to drop out of active regulation by ceasing to be a 'new drug.'

Weinberger v. *Hynson, Westcott & Dunning, Inc.*, *supra*, 412 U.S. at 631 (emphasis added).[31]

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[31] This Court's understanding that a drug would not cease to be a new drug until long after it had satisfied the requirements for FDA approval is substantiated by the statutory structure itself: 21 U.S.C. 321(p)(2) states that general recognition based on investigations to determine safety and effectiveness (the basis for approval of a new drug application) is not sufficient, absent use to a material extent and for a material time, to exempt a drug from "new drug" status.

It is further supported by the legislative history of the 1962 amendments. Thus, a witness before the Senate subcommittee quoted an FDA official as stating that, under the pre-1962 new drug provision: "Although there may be an effective new drug application for a product under which a drug firm is legally marketing it in interstate commerce, until there has been a considerable volume of distribution over a considerable period of time, it is still a new drug[;] * * * there can be no general recognition of safety by experts without appreciable use of the drug." *Drug Industry Antitrust Act: Hearings on S. 1552 Before the Subcomm. on Antitrust and Monopoly of the Senate Comm. on the Judiciary*, 87th Cong., 1st Sess. 63 (1961). This standard was confirmed when the 1962 amendments were passed. The Committee report suggests that "substantial evidence" of effectiveness, a prerequisite for approval of a new drug application, could exist even when experts generally did not know about the effectiveness studies or would disagree as to whether the drug was effective. See S. Rep. No. 1744 (Pt. 1), 87th Cong., 2d Sess. 16 (1962).

The court of appeals' assumption that approval equals non-"new drug" status, and thus exemption from the approval requirement, leads to irrational results inconsistent with the

4. The court of appeals apparently believed that if general recognition attached to products rather than active ingredients, no drug product could ever achieve "not new" status and the statutory distinction between a "new drug" and other drugs therefore would be "superfluous" (Pet. App. 7a). To the contrary, as this Court clearly contemplated in *Hynson*, it is possible for a drug product to achieve expert general recognition and pass out of "new drug" status at some point after being marketed for a period of time under an NDA. 412 U.S. at 631. The court of appeals' conclusion that a drug product could never become recognized as safe and effective was based on its incorrect assumption that recognition of a drug product's safety and effectiveness would require general expert knowledge of the ingredients and manufacturing processes of the product, which usually are trade secrets and would not become known to experts generally (Pet. App. 7a). In fact, published test results showing safety and effectiveness, on which expert general recognition is based, are tests of products—not active ingredients. Thus, experts can and do form opinions about a drug product on the basis of these tests without knowing how a drug was produced or what ingredients it contains.[32]

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statutory scheme. For example, if a pioneer drug were approved on one day, the generic copy then could escape the approval requirement the next day. The pioneer itself would, on the date of approval, cease to be a "new drug" and the withdrawal of approval provision of 21 U.S.C. 355(e) would be without effect.

[32]A lack of knowledge about inactive ingredients and manufacturing processes does, however, prevent expert general recognition of a generic copy based on testing of the *pioneer* product, because experts would not have adequate information

II. THE LEGISLATIVE HISTORY OF THE ACT CONFIRMS THAT GENERIC DRUG PRODUCTS ARE NOT EXEMPT FROM THE REQUIREMENT OF PREMARKETING APPROVAL

The legislative history of the new drug provisions of the 1938 Act, and of the 1962 amendments to those provisions, confirms that each drug product that has not itself achieved expert general recognition must be approved by the FDA before it is marketed.

A. The 1938 Act Was Intended by Congress to Prohibit the Marketing of Any Potentially Unsafe Drug Product

Prior to the passage of the Act in 1938, drugs could be marketed without any testing or governmental review. Following an incident in which numerous deaths were caused by the drug Elixir Sulfanilamide, however, Congress determined that removal of drugs from the market after they had caused harm simply was not an adequate means of protecting the public. It therefore enacted a system of premarketing review by FDA "to prevent the premature marketing of new drugs not properly tested for safety." H.R. Rep. No. 2139, 75th Cong., 3d Sess. 9 (1938).

Elixir Sulfanilamide was itself an untested drug composed of a widely used active ingredient and a new inactive ingredient; the *inactive* ingredient was responsible for the deaths caused by the drug.[33] Set

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to conclude the copy would not differ in bioavailability—and therefore in safety or effectiveness—from the tested pioneer drug.

[33] See *United States* v. *An Article of Drug . . . Bacto-Unidisk, supra,* 394 U.S. at 798; *AMP, Inc.* v. *Gardner,* 389 F.2d 825, 829-830 (2d Cir.), cert. denied, 393 U.S. 825 (1968);

against this historical background, it would be contrary to clear congressional intent for the requirement of premarketing review to be eliminated for generic drug products merely because they purport to contain the same active ingredient as other drugs that have been proved safe and effective. A statute with such an exemption would not have prevented the Elixir Sulfanilamide tragedy that first caused Congress to recognize the need for premarketing review.[34] Similarly, it would not protect the public from gen-

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S. Doc. No. 124, 75th Cong., 2d Sess. (1937); C. Dunn, *Federal Food, Drug, and Cosmetic Act, a Statement of Its Legislative Record* 1316-1327 (1938).

[34] Generix argues (Br. in Opp. 11) that "[a] lethal chemical is not an inactive ingredient," apparently suggesting that the "new drug" provision as interpreted by the court of appeals would prevent a repetition of the Elixir Sulfanilamide tragedy. This is incorrect.

The court of appeals held in this case that there can be no premarketing inquiry whatsoever into properties of a drug product if the identified active ingredient of the product is not a "new drug." In the case of Elixir Sulfanilamide, the manufacturer did not identify diethylene glycol, the lethal component, as an active ingredient in its product. In fact, of the ingredients in the product, only the active ingredient sulfanilamide was listed on its labeling. S. Doc. No. 124, *supra*, at 2. It follows that the manufacturer of Elixir Sulfanilamide, under the court of appeals' interpretation of the Act, could have marketed its product without preclearance merely because some other sulfanilamide product had been generally recognized as safe and effective.

Contrary to Generix's assertion (Br. in Opp. 11) that the legislative history of the 1938 Act never refers to diethylene glycol, the toxic component of Elixir Sulfanilamide, as an inactive ingredient, that history makes clear the congressional understanding that diethylene glycol was in fact an inactive ingredient. See S. Doc. No. 124, *supra*, at 1 (Elixir Sulfanila-

eric drug products that may be unsafe or ineffective because of their inactive ingredients. Therefore, generic drugs must be subject to the new drug provisions on a product-by-product basis to implement the Congressional determination that removal of unsafe drugs from the market after they have caused harm simply is not adequate to protect the public. See, *e.g.*, *United States* v. *Premo Pharmaceutical Laboratories, Inc.*, *supra*, 511 F. Supp. at 988-989.

B. The 1962 Amendments Did Not Exempt Generic Drug Products From The New Drug Approval Provisions Of The Act

1. The 1962 amendments to the Act were adopted in the wake of great public concern over thalidomide, a drug that had caused numerous cases of severe birth defects in European children whose mothers had taken that drug during pregnancy. Congress recognized that it was only because of the Act's premarketing clearance procedures that thalidomide was kept off the market in the United States.[35] There is nothing in the language or the legislative history of the 1962 amendments that suggests that Congress

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mide: Letter from the Secretary of Agriculture) (emphasis added):

> The lethal effect of the "elixir" was due to its content of diethylene glycol, which *was used as a solvent* in making a liquid preparation of sulfanilamide, usually administered in tablet or powder form. Sulfanilamide itself is a valuable drug, and was not responsible for the disaster.

See generally *ibid.*, *passim*; C. Dunn, *Federal Food, Drug, and Cosmetic Act, A Statement of Its Legislative Record*, *supra*, at 1316-1327.

[35] See, *e.g.*, S. Rep. No. 1744 (Pt. 2) 87th Cong., 2d Sess. 1 (1962); 108 Cong. Rec. 14677-14680, 16316-16317, 16322-16325, 19897-19898, 19909, 22037-22038, 22047-22048 (1962).

meant to weaken the new drug provisions by exempting generic drugs from the premarketing approval requirements of 21 U.S.C. 355.

2. To protect the public from ineffective drug products, Congress amended the Act to prohibit the marketing of drugs whose effectiveness has not been established.[36] Thus, Congress added to the statutory requirement of adequate testing to show *safety* the further requirement that substantial evidence of *effectiveness* must be demonstrated. A corresponding change was made in the definition of "new drug"; drugs cannot escape "new drug" status unless their effectiveness as well as their safety is generally recognized by qualified experts.

The amendment of the Act and Congress' desire to promote the use of generic drug products did not, as the court of appeals thought, mean that Congress intended to exempt generic products from the approval process. Senator Kefauver himself, in first proposing the amendment of the new drug provisions to require that FDA review products for effectiveness as well as safety, premised his proposal on his understanding that the review would be on a product-by-product basis. Only if FDA reviewed the effectiveness of each product, he argued, could generic brands compete effectively with pioneer products:

> Despite the fact that different brands are identical generically, the contention was made at the hearings that identical products which met the safety requirements of the law, nevertheless, were for various reasons not equal in therapeutic quality or efficacy. I am satisfied that much of the high cost of drug products has come about as a

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[36] See H.R. Rep. No. 2464, 87th Cong., 2d Sess. 1 (1962); S. Rep. No. 1744 (Pt. 1), 87th Cong., 2d Sess. 8 (1962).

> result of this claim, whether it is fact or fiction. Hence, the requirement of this bill that the Food and Drug Administration pass on the efficacy as well as the safety of new drugs should make it more difficult to contend successfully that there is a difference between two brands which are identical generically and both cleared as to safety and efficacy. Thus, promotion costs of new drugs attributable to this contention could be saved and the price of new drugs lowered accordingly.

106 Cong. Rec. 12665 (1960).

Congress also increased the protection afforded the public by eliminating the procedure whereby an NDA became effective automatically in the absence of FDA action to disapprove it. Under the Act as amended, "a new drug application is not effective unless it has affirmative approval both for safety and effectiveness." H.R. Rep. No. 2464, 87th Cong., 2d Sess. 10 (1962). See also S. Rep. No. 1744 (Pt. 2), 87th Cong., 2d Sess. 4-5 (1962).

3. Contrary to the court of appeals' interpretation (Pet. App. 10a-12a), the addition of the "established name" labeling requirements (21 U.S.C. 352(e))[37] does not indicate any Congressional intent

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[37] 21 U.S.C. 352(e) requires that the common names of the active ingredients and of certain inactive ingredients of a drug be stated on the label of the drug. This information, of course, would not be sufficient to allow a doctor or pharmacist to determine whether a generic drug would have the same effect on the patient as the pioneer. See pages 19-22, *supra*.

Contrary to the court of appeals' assumption that drugs "obtain an 'official' or 'generic' name through general recognition" (Pet. App. 12a), the concept of "general recognition" relates only to the definition of "new drug." It does not appear in the labeling provisions of 21 U.S.C. 352(e), and has nothing to do with the assignment of generic names.

to permit the marketing of potentially unsafe or ineffective generic drug products. Rather, Congress sought to facilitate substitution only of *safe and effective* generic drugs,[38] thereby encouraging cost savings and competition in the drug industry.[39] Congress assumed that *no* drug—pioneer or generic—would reach the market unless its safety and effectiveness were established through general recognition or an approved NDA.[40] There is nothing in the legislative history to support the view that Congress intended to subject the public to the risk that generic

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[38] Inclusion of the established name for a drug's active ingredient in its labeling assists doctors and pharmacists in identifying generic equivalents and "ascertain[ing] the qualities and specifications of the products and the competing products." S. Rep. No. 1744 (Pt. 1), *supra*, at 18. Labeling a drug with the generic name as well as the trade name aids physicians in deciding "whether to prescribe by the trade name upon which they have come to rely or to prescribe the so-called generic equivalent by using the official name or by authorizing the pharmacist to select a product bearing the official name" (*ibid.*).

[39] Moreover, much of the discussion in the legislative history of the need to improve competition related to proposals—never enacted—that would have limited the terms of drug patents. Proponents of those proposals recognized that, as reported, the 1962 amendment "will have only a very limited effect on prices * * *. Its major result will be to improve the quality of drugs." S. Rep. No. 1744 (Pt. 1), *supra*, at 33.

[40] See, *e.g.*, 108 Cong. Rec. 17366 (1962) (emphasis added):

> [E]very brand new *product*, and every new claim for an existing product, would be subject to the tests and procedures established in [21 U.S.C. 355].

Contrary to the court of appeals' assertion (Pet. App. 9a), this reference is fully consistent with—rather than contrary to—the plain language and logic of the Act.

drug products, while they might be lower priced, would not be safe and effective.

III. PREMARKETING APPROVAL OF GENERIC DRUG PRODUCTS IS NECESSARY TO EFFECTUATE THE FUNDAMENTAL PURPOSE OF THE ACT

A. Premarketing Review Is The Only Means By Which FDA Can Protect The Public From Unsafe Or Ineffective Generic Drug Products

Narrowing the definition of "drug" to exempt generic drug products from the new drug approval requirements, as the court of appeals has done, is contrary not only to the specific statutory language and legislative history discussed above but also to the fundamental principle—protection of the public health—that has guided the courts in interpreting the Act. As this Court noted in *United States* v. *Dotterweich*, 320 U.S. 277, 280 (1943):

> The purposes of [the Act] * * * touch phases of the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self-protection. Regard for these purposes should infuse construction of the legislation if it is to be treated as a working instrument of government and not merely a collection of English words.

See also *Kordel* v. *United States*, 335 U.S. 345, 349 (1948); *United States* v. *Sullivan*, 332 U.S. 689, 696 (1948).[41] Moreover, as this Court has held: "Congress fully intended that the Act's coverage be

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[41] The lower courts have also applied this basic principle in construing the Act. See, *e.g.*, *United States* v. *Naremco, Inc.*, 553 F.2d 1138, 1141 (8th Cir. 1977); *Upjohn Co.* v. *Finch*, 422 F.2d 944, 947 (6th Cir. 1970); *Carter-Wallace, Inc.* v. *Gardner*, 417 F.2d 1086, 1094-1095 (4th Cir. 1969), cert. denied, 398 U.S. 938 (1970); *United States* v. *Vitasafe Corp.*, 345 F.2d 864, 870 (3rd Cir.), cert. denied, 382 U.S. 918 (1965).

as broad as its literal language indicates—and * * * broader than any strict medical definition might otherwise allow." *United States* v. *An Article of Drug . . . Bacto-Unidisk*, *supra*, 394 U.S. at 798. See also *United States* v. *Rutherford*, 442 U.S. 544 (1979). To exempt generic drug products from premarketing review would be contrary to the Act's basic intent because it would remove the *only* effective means of protecting the public from potentially unsafe or ineffective generic drugs.

1. As we have shown (pages 19-22, *supra*), because of differences in their ingredients, methods of compounding, and therapeutic effect, FDA review of pioneer drugs does not insure that generic drugs are safe and effective. Nor could FDA's power to institute post-distribution enforcement actions prevent the marketing of unsafe or ineffective generic drugs if premarketing approval were not required. Indeed, if FDA had to institute an enforcement action and demonstrate that an unapproved generic drug product was in fact unsafe or ineffective, the burden of proving safety and effectiveness that Congress placed squarely on manufacturers would be reversed, and unsafe or ineffective products could be marketed to the detriment of the public until FDA gathered the requisite evidence and instituted enforcement actions.

Generix's argument (Br. in Opp. 27) that the government should be required to establish that specific unapproved drugs are harmful harks back to the days prior to the 1938 passage of the new drug provisions, when potentially harmful drugs could be placed on the market with impunity until the government was able to prove them unsafe. Under current law, however, it is clear that when the "new drug" status of a drug is at issue, the government has no burden to show that the drug is in fact unsafe or

ineffective.[42] For this reason, the actual safety and effectiveness of the drug is irrelevant to the question whether the drug is "generally recognized" as safe and effective. See, *e.g.*, *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, *supra*, 629 F.2d at 803-804; *United States* v. *1,048,000 Capsules . . . Afrodex*, 494 F.2d 1158, 1160 (5th Cir. 1974); *Tyler Pharmacal Distributors, Inc.* v. *United States Department of Health, Education & Welfare*, 408 F.2d 95, 99 (7th Cir. 1969).

2. Contrary to the court of appeals' assumption (Pet. App. 13a-14a), the adulteration provisions of the Act, 21 U.S.C. 351, as amended in 1962, also are inadequate to prevent the marketing of unsafe or ineffective generic drugs "without subjecting the drug product to the new drug approval process" (Pet. App. 13a). The new drug approval requirement and the requirements of 21 U.S.C. 351 address two different problems, and *both* are necessary to protect the public health.[43]

By requiring the applicant to describe the components of a new drug and the process by which it is manufactured, and to present evidence that that drug is safe and effective, 21 U.S.C. 355(b) assures that

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[42] There is no doubt, however, that some unapproved generic drugs *are* dangerous. The *Premo* court found that some of the drugs Premo made (which Generix distributed), if not bioequivalent to the pioneers they copied, could cause death or irreversible disfigurement in patients treated with those drugs. 511 F. Supp. at 992-993, 994-995. See also Tr. 47-48.

[43] This issue was explicitly explored in *United States* v. *Premo Pharmaceutical Laboratories, Inc.*, *supra*. The court there found that compliance with FDA's good manufacturing practice regulation would not protect the public from drugs that were not bioequivalent. 511 F. Supp. at 989; *id.* at 976-977.

FDA will receive the information it needs to determine whether the product described in an NDA is safe and effective. The complementary purpose of the adulteration provision, 21 U.S.C. 351, is to assure that every batch of the drug product as manufactured *is* the product whose safety and effectiveness have been demonstrated in the NDA or by expert recognition. Thus, 21 U.S.C. 351 provides that a drug is "adulterated" and may not be marketed if it does not have the safety, identity, strength, quality and purity characteristics the product purports or is represented to possess.[44]

Under the 1938 Act, FDA had only limited power to protect the public from drugs that were adulterated because of deficiencies in strength, quality or purity. The enforcement tools available to the government—seizure, injunction, and criminal prosecution—could not be used until offending products had been marketed; even then the government had to prove that the product was deficient. In 1962, therefore, Congress expanded the adulteration provisions to prohibit the marketing of drugs by manufacturers who did not adhere to good manufacturing practices, *i.e.*, the procedures necessary to assure that the manufacturer follows its "recipe" in producing a drug product. 21

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[44] Nor, contrary to the court of appeals' apparent assumption (Pet. App. 13a), is the requirement of 21 U.S.C. 351(b) an adequate substitute for premarketing approval. That provision requires that a drug that purports to conform to standards set out in an official compendium in fact meet that compendium's standards. Those standards are not designed to assure bioequivalence. Accordingly, compliance with the compendial standards would not assure that a generic copy could be safely substituted for a pioneer. See Tr. 98-100; see also *United States* v. *Premo Pharmaceutical Laboratories, Inc.*, *supra*, 511 F. Supp. at 987, 988-989, 977.

U.S.C. 351(a)(2)(B).[45] So that FDA could enforce the good manufacturing practices requirement, Congress increased FDA's authority to inspect prescription drug manufacturers, 21 U.S.C. 374(a), and required manufacturers periodically to register with FDA, 21 U.S.C. 360.[46]

The adulteration prohibitions, even with the addition of the good manufacturing practices provision, however, provide no mechanism for assuring that a generic drug product's effect will be the same as that

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[45] A drug is adulterated under 21 U.S.C. 351(a)(2)(B) if the "methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess." See 211 C.F.R. Parts 210-211.

[46] As reported by the subcommittee, the bill that became the 1962 amendments "would have set up a registration system [for drug manufacturers] which * * * would have in effect constituted a licensing system." S. Rep. No. 1744 (Pt. 1), *supra*, at 12; see S. 1552, 87th Cong., 1st Sess., as introduced by Senator Kefauver on April 12, 1961. The full committee deleted the licensing provision. The congressional rejection of a "licensing" system on which respondents (Br. in Opp. 15) rely, was a rejection of this *manufacturer* licensing provision; it does not indicate any congressional intent to exempt generic drugs from a product-by-product application of the "new drug" approval requirements.

The court of appeals referred to a statement in the legislative history of the 1938 Act that the new drug provision "is not a license provision" (Pet. App. 9a, quoting H.R. Rep. No. 2139 (Pt. 1), 75th Cong., 3d Sess. 9 (1938)). This statement, which is not otherwise explained, may refer also to the rejection of a *manufacturer* licensing provision that some members of Congress had sought in 1938. See 83 Cong. Rec. app. 2279 (1938) (remarks of Rep. Coffee).

of a pioneer drug product containing the same active ingredient. Nothing in 21 U.S.C. 351 or in the related FDA regulations (21 C.F.R. Parts 210-211) prohibits differences in inactive ingredients or methods of compounding that may cause generic products to have effects on the patient different from those of the pioneer drug. *United States* v. *Premo Pharmaceutical Laboratories*, *supra*, 511 F. Supp. at 980.[47] If differences between the "recipe" for a generic drug and that for the pioneer result in a lack of bioequivalence between the two drugs, that problem obviously is not cured by the generic drug manufacturer's careful adherence to the generic drug recipe. Thus, the good manufacturing practices requirements simply are not a substitute for premarketing review of safety and effectiveness of each individual generic drug product.

B. Premarketing Approval of Generic Drug Products Promotes Rather Than Impairs Competition in the Marketing of Safe and Effective Generic Drugs

The court of appeals (Pet. App. 9a-11a) also was incorrect in its assumption that exempting generic drug products from the Act's "new drug" premarketing approval requirements is necessary to effectuate the Congressional purpose of improving competition in the drug industry. To the contrary, generic prescription drugs would be *less* likely to compete effectively with pioneer drugs if the public were deprived of the safeguards afforded by FDA premarketing review.

1. It is not necessary to exempt generic drugs from the new drug provisions of the Act in order to allow

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[47] Indeed, as the court of appeals noted (Pet. App. 7a), the formulation of the pioneer drug usually is a trade secret and may not be revealed by FDA. See 21 U.S.C. 331(j).

competitive marketing of safe and effective generic drugs. Indeed FDA has sought to minimize the burden of filing and obtaining approval of generic drug NDAs to the extent consistent with insuring that the public is not subjected to unsafe or ineffective drugs.[48]

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[48] Generix argues (Br. in Opp. 18-22), and the court of appeals apparently agreed (Pet. App. 8a n.4), that FDA's interpretation of the Act's new drug provisions is not entitled to the deference usually afforded its interpretation of the Act (*e.g., United States* v. *Rutherford, supra*) because it has not been consistent. This argument is essentially irrelevant since the plain language of the Act and its legislative history compel the conclusion that the Act's "new drug" requirements apply to generic drug products.

At all events, Generix and the court of appeals have seriously distorted the FDA's actions. Contemporaneously with the passage of the 1938 Act, the Secretary of Agriculture (who then had responsibility for enforcement of the Act) promulgated a regulation that made it clear that a drug could be considered a "new drug" if there were any change in, *inter alia*, the inactive ingredients from which it was formulated (see 3 Fed. Reg. 3161-3162 (1938)). That regulation stating the agency's official interpretation of the "new drug" definition (now 21 C.F.R. 310.3(h)) has remained substantially unchanged to the present day.

The FDA's practice, initiated during World War II and terminated in 1968 (33 Fed. Reg. 7758 (1968)), of informing drug manufacturers that they did not need to submit new drug applications for certain drugs because those drugs were not "new drugs" (Pet. App. 8a n.4) was not a statement that generic copies of approved drugs automatically would escape "new drug" status. Indeed, some generic copies of approved drugs were seized and condemned as unapproved new drugs during the time this practice was in effect. See 40 Fed. Reg. 26142, 26143 (1975). Arguably, the so-called "not new drug" letters reflected FDA's understanding that experts at that time would recognize the safety of generic products on the basis of less evidence than experts today would require in light of developing knowledge about the importance of inactive ingredi-

For many generic prescription drugs, FDA has determined that complete safety and effectiveness studies need not be submitted by each manufacturer in order to satisfy the requirements of 21 U.S.C. 355(d). Instead, manufacturers of certain generic drugs may obtain FDA approval by submitting an abbreviated new drug application ("ANDA"). See 21 C.F.R. 314.1(a) and (f).[49] Under this procedure, the manu-

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ents' effect on bioavailability. Cf. *United States* v. *Western Serum Co., Inc.*, 666 F.2d 335, 339-341 (9th Cir. 1982) (expert general recognition must be current).

Moreover, to the extent "not new drug" letters indicated that generic drug products could be marketed without FDA approval, those letters may be viewed as inconsistent with the Act and with this Court's decision in *Weinberger* v. *Hynson, Westcott & Dunning, Inc., supra*, 412 U.S. at 624. See *United States* v. *Articles of Drug . . . Hormonin*, 498 F. Supp. 424, 436 (D.N.J. 1980), aff'd without opinion, No. 81-1035 (3d Cir. Sept. 15, 1981). Even if the FDA's past practice is considered to conflict with its present position, therefore, that past practice binds neither it nor this Court.

FDA's current abbreviated new drug application procedures (see pages 40-41, *infra*) simplify the requisite proof of safety and effectiveness for generic drugs, but they do not permit deviation from the statutory requirement of premarketing approval for each drug product, based on evidence that that drug product itself is safe and effective.

[49] The ANDA process currently applies only to copies of drug products for which the FDA has published a notice known as a Drug Efficacy Study Implementation ("DESI") Notice. Most, but not all, of the unapproved drugs Generix was distributing purported to be generic copies of drugs subject to such notices and the manufacturers therefore could have sought approval under this simplified procedure.

In addition, the FDA is implementing a so-called "paper NDA" policy for post-1962 generic drugs, 45 Fed. Reg. 82052 (1980); 46 Fed. Reg. 27396 (1981). Under that policy, applicants may rely on the scientific literature, if it provides ade-

facturer may establish that the generic prescription drug is safe and effective by showing that it contains the same active ingredient as an approved new drug, and *also* that the effect of the generic drug on the patient is equivalent to that of the approved drug. In effect, therefore, FDA relies in part on the body of knowledge developed for the pioneer drug product in evaluating the ANDA. If the manufacturer of the generic drug shows that there are no differences between the approved drug and the "me-too" drug that will result in differences in safety or effectiveness, the generic drug is deemed to have the requisite evidence of safety and effectiveness. If the other requirements are also satisfied, the ANDA is approved.[50]

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quate data, to establish safety and effectiveness of a pioneer drug. Safety and effectiveness of a generic drug is then established by such literature *plus* the applicant's showing that its generic drug is bioequivalent to the pioneer. 21 C.F.R. 320.22. In an attempt to facilitate further the approval of safe and effective generic drug products, FDA also is exploring the possibility of authorizing use of ANDAs for copies of drugs approved after 1962 and thus not covered by DESI notices. See 47 Fed. Reg. 1765 (1982).

[50] Contrary to Generix's assertion (Br. in Opp. 3 n.5), FDA's procedures for regulating over-the-counter (OTC) drugs are not at issue in this case. The government sought an injunction because of its concern about Generix's distribution of unapproved *prescription* drugs; the evidence presented to the district court was limited to prescription drugs; and neither the district court nor the court of appeals addressed the separate issue of OTC regulation.

Nor would a holding that the Act's new drug approval procedures apply to generic drug products invalidate FDA's current OTC drug regulations (21 C.F.R. Part 330). The OTC regulations themselves deal with drug products, rather than only active ingredients, although the analysis of OTC products is done on the basis of classes of active ingredients. Thus, for

2. If generic drugs were not subject to premarketing approval, however, a physician or pharmacist would have no assurance that generic products were as safe and effective as the brand name drugs for which they purport to be substitutes. Therefore, as the government's experts testified in this case (Tr. 55-57), careful doctors and pharmacists, if they became aware that generic drugs were not subject to premarketing review, would be deterred from prescribing generic drugs regardless of the cost savings that might be obtained.[51]

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example, "[a]n over-the-counter antacid *product*" (emphasis added) that complies with the antacid monograph is regarded by the agency as generally recognized as safe and effective and not misbranded. 21 C.F.R. 331.1. There is no agency finding that any active ingredient itself is generally recognized as safe and effective or is not a new drug. Moreover, to the extent that there are differences between FDA's treatment of prescription and OTC drugs, they are warranted by practical considerations. Lack of bioequivalence between different OTC products containing the same active ingredients presents less danger than a similar lack in prescription drugs because OTC drugs, in contrast to prescription drugs (see 21 U.S.C. 353 (b)(1)), are intended for the treatment of minor, and in many cases self-limiting, conditions. Thus the monographs, which limit the amount of OTC drugs' active ingredients to levels that pose no risk of toxicity and impose standards with respect to inactive ingredients, are a reasonable means of coping with the necessity of regulating between 100,000 and 500,000 OTC products. See 37 Fed. Reg. 85 (1972). See also *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, *supra*, 412 U.S. at 650-651. In addition, FDA's treatment of OTC drugs is consistent with the statute's definition of "new drug": experts generally require more information about prescription drug products before determining that they are safe and effective than those experts would require of an OTC preparation.

[51] See also *Pharmadyne Laboratories, Inc.* v. *Kennedy*, *supra*, 466 F. Supp. at 106.

Since current law prohibits the labeling of any drug with a notice that it has (or has not) been approved by FDA, 21 U.S.C. 331(*l*), the exemption advocated by respondents and adopted by the court below would have a negative impact on sales of generic drugs—including those that have been shown to be safe and effective and have been approved by FDA. Unless the decision below is reversed, the only way to be assured of using a safe and effective product would be for doctors to specify and pharmacists to dispense only the pioneer. Such a result would be contrary to the very congressional policy of increased competition that the court of appeals thought supported its decision. Moreover, it would hamper efforts by the FDA, other federal government agencies, and state governments to foster the use of safe and effective substitutes for more costly prescription drugs.[52]

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[52] Generally, drug substitution programs, both in the states and in the federal system, allow a physician to veto substitution. For example, under the federal "maximum allowable cost" regulations implementing the Medicare and Medicaid reimbursement statutes, a physician may, by so stating on his prescription, veto substitution, 45 C.F.R. 19.3(a)(3). Physicians may be expected to veto substitution where they cannot be assured that all generic copies of the products they are prescribing have been approved by FDA. For a discussion of state substitution programs and the effect of the generic "new drug" issue on those programs, see *Pharmadyne Laboratories, Inc.* v. *Kennedy, supra*, 466 F. Supp. at 106. Cf. Note, *Consumer Protection and Prescription Drugs: The Generic Drug Substitution Laws*, 67 Ky. L.J. 384 (1978-1979).

CONCLUSION

The decision of the court of appeals should be reversed.

Respectfully submitted.

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in the Supreme Court of the United States

OCTOBER TERM, 1981

UNITED STATES OF AMERICA,
Petitioner,

versus

GENERIX DRUG CORPORATION, *ET AL.*,
Respondents.

**On Writ of Certiorari to
The United States Court of Appeals
For the Eleventh Circuit**

BRIEF FOR GENERIX DRUG CORPORATION, *ET AL.*

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QUESTION PRESENTED

Whether all generic drug products, including over-the-counter products, require premarket approval by the FDA when they contain active ingredients which are generally recognized as safe and effective?[1]

[1]Respondents adopt and incorporate the statement of parties contained in Petitioner's brief at I.

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STATEMENT

The Government's[2] Statement is fair and accurate to the extent that it presents the testimony of certain witnesses and the nature of the proceedings below. Generix disagrees with some of the legal conclusions in the Government's statement but will address those arguments in the argument section of its brief. The Government's statement is somewhat incomplete. Generix supplements the Government's statement in accordance with SUP. CT. R. 34.2.

Generix is a pharmaceutical company engaged in the business of distributing[3] high quality generic drugs at reasonable prices. A generic drug is a drug product with the same active ingredients as a brand name drug product. All of the products that Generix distributes are generic formulations of products which have been marketed for many years, often for decades, under approvals granted by the FDA for brand name versions of those products. The principal difference to the consumer between a brand name drug product and a generic version of the same product is that the generic costs considerably less than the brand name. Generix' products cost approximately one-half the price that is charged for the same product under a brand name. (R. 197).

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[2]Petitioner United States of America will be referred to as the Government. Respondents will be referred to collectively as Generix. Respondents adopt the record abbreviations used by the Government. "GB" will be used to refer to the Government's brief on the merits. All emphasis is supplied by counsel unless otherwise indicated.

[3]Generix does not manufacture the products it sells. It obtains them from pharmaceutical companies which specialize in making generics. (R. 198).

The Government filed suit seeking to prohibit the sale of some of the products Generix distributes. The Government did not take the position or adduce any evidence to show that Generix' products were unsafe. Rather, the FDA's position was that the products were "new drugs" under 21 U.S.C. § 321(p) which required approval by the FDA by way of a "new drug application" ("NDA"). Only products that are new drugs under 21 U.S.C. § 321(p) require an NDA as a condition of marketing.[4]

The pharmaceutical industry is divided over the legal issue involved in this suit. The NDA requirement is a barrier to drug market entry. Approval is costly to

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[4]Both the Government and The Proprietary Association as amicus curiae have claimed that the issue presented here involves only prescription products. That claim is incorrect. The complaint sought an injunction against the distribution of all unapproved new drugs, not merely unapproved prescription products. (J.A. 17). After the hearing on the preliminary injunction, the Government sought discovery to determine the extent of the relief it would seek against Generix at the final hearing. It propounded interrogatories asking Generix to identify "every unapproved new drug product" which it distributed. Generix produced a copy of its catalogue to the Government. It reveals that Generix distributes a complete line of over-the-counter ("OTC") non-prescription products including vitamins, cold capsules and aspirin. Generix' Fifth Circuit brief discussed this aspect of the case. Generix' Fifth Circuit Brief at 26-28. At oral argument in the Fifth Circuit, the court was concerned that a ruling in the Government's favor would require manufacturers to obtain approval of NDAs before marketing new generic aspirins. The Government's attorney conceded that a ruling in his favor would lead to this result. The Fifth Circuit's holding is not confined to prescription drugs. It extends to all drug products. *United States v. Generix Drug Corp.*, 654 F.2d 1114, 1115, 1120 (5th Cir. 1981). Even if, by some stretch of the imagination, the issue were not directly involved here, it would be important to keep in mind that a ruling in the Government's favor would affect both prescription and non-prescription products since the new drug provisions of the Act do not distinguish between them.

obtain and is frequently granted only after substantial administrative delays. NDA proceedings can take several years.[5] The FDA's position, by reducing competition, favors larger companies, especially the brand name manufacturers with existing NDAs, over smaller companies which would need FDA approval before marketing competitive and cheaper products using the same drugs.[6] The losers in this tug-of-war are consumers, who must pay higher prices for brand name products unless a generic is available. In some cases, there is only one brand name version of a drug and the only competition is provided by generic versions of the same drug. (R. 204-05).

At the hearing on the preliminary injunction, the Government introduced evidence concerning the following drugs: allopurinol, spironolactone with hydrochlorothiazide, furosemide, diethylpropion hydrochloride, chlorothiazide with reserpine and amitriptyline with perphenazine. (R. 379).[7] Each of these

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[5]It has been estimated that the total amount of time involved from synthesis of a new chemical entity to NDA approval averages 13 years. Final Report, Comm'n on the Federal Drug Approval Process (Mar. 31, 1982).

[6]The presence of one trade association representing several generic manufacturers as an amicus curiae in support of the Government's position is not inconsistent with this observation. The manufacturers comprising this group have significant numbers of approved abbreviated new drug applications ("ANDAs") for the generic products they manufacture. Their interest, like that of the name brand manufacturers, is to restrict competition among the manufacturers of generics.

[7]The Government did not introduce any evidence concerning prochlorperazine maleate or chlorthalidone. (R. 379). Generix was not enjoined from distributing these drugs. (R. 388). The trial court named some drugs incorrectly in its preliminary injunction and enjoined distribution of specific products which already had

drugs is marketed under a brand name formulation which has an approved NDA. (R. 199). All of these active ingredients are generally recognized among qualified experts as safe and effective. Each has been used to a material extent and for a material time for the uses recommended in the labeling employed by Generix. (R. 212-24). Each drug has been widely used and is well known although studies on the specific combination of chlorothiazide with reserpine are not readily available. (R. 212-24).

The Government did not introduce evidence that the formulations of these drugs which Generix distributes are unsafe. It did not even introduce evidence that the generic formulations were different than the brand name formulations. Rather, the Government limited itself to showing that Generix' specific formulations containing these active ingredients had not been tested and were not generally recognized among experts qualified by specific training and experience to evaluate the safety and effectiveness of drugs as safe and effective under the conditions of use prescribed, recommended or suggested in Generix' labeling. E.g., (R. 49-50).[8] Generix' expert testified to the contrary. (T. 227). Moreover, he testified that expert opinions about whether a product

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approved ANDAs. Generix sought alternative relief in the form of modification of the preliminary injunction on these grounds on appeal. The Government did not oppose this request. The Fifth Circuit did not reach the modification issues. If this Court reverses the Fifth Circuit, remand for consideration of these issues would be appropriate.

[8]This testimony was circular. Government experts testified that Generix' products were not generally recognized as safe and effective because those specific formulations did not have FDA approval. (T. 60). Conversely, they recognized products as safe and effective simply because they had FDA approval. (T. 63).

is safe and effective "invariably reflect" an opinion on the active ingredient in the product and not on the product itself since the experts do not have manufacturing information. (T. 212-13). Even the Government expert admitted that if it were necessary for the community of experts to have specific information about the way a particular product was manufactured before it concluded that the product was safe and effective, most products would not be recognized as safe and effective. (T. 62-64).

The Government also introduced evidence about the manner in which products are formulated. A drug product is composed of an active ingredient, or incipient, which represents up to 10% of the product, and excipients, such as binders, coating and capsules, which account for the remainder. Variances in the excipients can affect the bioavailability of the active ingredient and the bioequivalence of various drug products. (R. 380).[9] The Government experts testified that differences in bioavailability and bioequivalence between an approved product and a generic copy may affect the safety and efficacy of the generic. (R. 380-81). However, there was no evidence that any differences between the approved products and the Generix formulations made the Generix formulations unsafe or ineffective. (T. 72).[10]

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[9]Bioavailability is a measure of the time it takes for a given product to deliver the active ingredient to a particular organ or area of the body. 21 C.F.R. § 320.1(a). Bioavailability is affected by inactive ingredients and manufacturing techniques, among other things. Bioequivalence is a measure based on a comparison of one product with another. Products which are bioequivalent can be used interchangeably for the treatment of the same condition or illness. (R. 380).

[10]This logically followed from the Government's failure to show that there were any differences at all.

There are various mechanisms in the law designed to deal with this problem. (T. 214). The United States Pharmacopoeia [USP] and The National Formulary [NF] contain standards to guarantee the identity, strength, quality and purity of drugs that are listed in them. (T. 215). All of the drugs in this case are listed in the USP and NF. (T. 215). These standards relate to how to get the active ingredient into the body. (T. 215). If a product does not meet these criteria, it is considered adulterated. (T. 216). The FDA has the power to regulate the sale of adulterated drug products. (T. 155-56).

After reviewing the evidence, the trial judge rejected the Government's position that an NDA is required for each new generic drug product. He rejected Generix' position that no generic product is a "new drug" requiring FDA approval if the active ingredient is generally recognized as safe and effective. He ruled that a generic manufacturer is entitled to sell a generic product without FDA approval if the evidence shows no reasonable possibility that differences in the excipients between a recognized and a generic product will make the generic product less safe and effective than the recognized product. He found that the Government had demonstrated a reasonable possibility that differences between certain Generix products and brand name products might affect the safety and effectiveness of the Generix products. He enjoined Generix from distributing products which contained six active ingredients. (R. 377-88).

Generix appealed. It argued on the basis of the Act, its legislative history and the FDA's own prior interpretation of the Act that a product was not a new drug if it contained active ingredients which were generally recognized as safe and effective. The Fifth Circuit agreed with Generix. *United States v. Generix Drug Corp.*, 654 F.2d 1114 (5th Cir. 1981). It held that a

drug product is not a new drug if the active ingredients in the product satisfy the requirements of 21 U.S.C. § 321(p). The court based its decision on several factors. First, it relied on the plain words of the statute and the interplay between 21 U.S.C. §§ 321(g)(1) and (p). The court correctly reasoned that § 321(p) would be totally superfluous if, as the Government claimed, all drug products containing the same active ingredients were "new drugs." It reviewed the legislative history of the 1938 Act and the 1962 amendments. The court found that the FDA's interpretation of the Act would create a product-by-product licensing system, a conclusion which was against clear Congressional intent.

At some point after the Government filed suit, Generix stopped selling products which did not have approved NDAs or ANDAs. However, until very recently, Generix was attempting to recover unapproved products which the Government had seized. On January 18, 1982, this Court stayed a district court order requiring return of the seized unapproved products pending appeal. *United States v. Undetermined Quantities of Articles of Drugs*, No. A-617 (S.Ct., Jan. 18, 1982). As a result of the stay order, the shelf lives of most of the seized products have expired or will expire before appellate review in the seizure actions is complete.[11] Generix is therefore abandoning its claim to these products. The appeal in the seizure cases is moot. Generix has so informed the Eleventh Circuit. Generix has also consented to the entry of a permanent injunction against it. Generix believed that these subsequent developments mooted this case. It filed a suggestion of mootness in this Court. This Court rejected Generix' contention.[12]

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[11]Counsel has recently been informed that the United States Marshall has destroyed all of the seized products with expired shelf lives or shelf lives of less than three months.

this case. It filed a suggestion of mootness in this Court. This Court rejected Generix' contention.[12]

SUMMARY OF ARGUMENT

The central issue in this case is the Government's contention that certain products Generix formerly distributed are unapproved "new drugs." A "new drug" must be approved by the FDA in the form of an NDA issued in accordance with 21 U.S.C. § 355. Not all products require an approved NDA as a condition of marketing. Only products that are "new drugs" must be approved. The Act defines a "new drug" as a drug that is not "generally recognized" among experts as safe and effective, or that has not been marketed to a material extent or for a material time. 21 U.S.C. § 321(p).

The products at issue in this case are not "new drugs." Rather, they are generic products containing drugs that have been widely marketed for many years and are broadly acknowledged in the medical community to be safe and effective. (R. 215). The products in question are subject to the Act's provisions relating to good manufacturing practices, adulteration and conformity with compendial standards. 21 U.S.C. § 351.

Although the Government has attempted to portray its case against Generix as merely the routine application of settled principles of law, this action is in reality based on a novel and controversial theory. The Government's theory holds that *each product* formulated

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[12]Generix does not know whether this Court's rejection of its suggestion of mootness precludes it from raising the issue at oral argument when this Court considers the merits of the case. Generix intends to pursue its mootness argument if this Court allows it to do so.

by *each manufacturer* is a "new drug," although the active ingredient in the product is not a "new drug." Under this theory, whenever a manufacturer undertakes to market a product with the same active ingredients as an approved brand name product, it must obtain approval of an NDA. Individual product approval is necessary, according to the Government, because different manufacturers make products in different ways, and these manufacturing variations *may* affect the way in which the products perform. The Government did not allege or prove that any of the products Generix distributes performs differently from its brand name counterpart.

The Government's theory is belied by the Act, its legislative history and the FDA's interpretation of the Act for over 30 years. It reads the "new drug" definition and the adulteration provisions out of the Act. Because the information that might influence an expert's opinion of the performance characteristics of individual products is incapable of achieving "general recognition" among experts in drug safety and effectiveness (R. 222-23), all products would be "new drugs" under the Government's approach.

Behind the Government's suit against Generix is a regulatory philosophy sharply tilted in the direction of maximum FDA control over the marketing of drug products. From the FDA's point of view, the ideal legal system for prescription drug products would include a requirement that every manufacturer and every individual product be licensed by the FDA. In this ideal system, the FDA would have an opportunity to determine, in advance of marketing, whether all products were properly made. The FDA has proposed legislation that would create the system just described by modifying drastically

the law that exists now.[13] It is the present law, however, not the one proposed by the FDA, that governs the disposition of this case. The Fifth Circuit's decision should be affirmed.

ARGUMENT

GENERIX' PRODUCTS ARE NOT NEW DRUGS. THEY DO NOT REQUIRE PREMARKET CLEARANCE.

A. The Active Ingredients In Each Of Generix' Products Are Generally Recognized As Safe And Effective.

The Government sets up a straw man and knocks him down. It claims:

> In arguing that [its products] were not [new drugs], Generix relied on the fact that FDA had approved other drug products containing the same active ingredients as Generix' drugs.

(GB. 4-5). This characterization of Generix' position is incorrect. Generix' position is that its products do not require premarket clearance because their active ingredients are generally recognized as safe and effective.

Each of the drugs which was covered by the district court's injunction is a well-known and widely-prescribed drug that has been available to the medical community for many years. (R. 215). Each drug is the subject of published scientific literature demonstrating its safety and effectiveness for therapeutic use under the conditions recommended in the labeling of the products Generix distributes. (R. 216-22). All of the drugs are recognized

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[13]See S. 1075, 96th Cong., 1st Sess. (1979), discussed *infra* at 34.

in the USP or a comparable drug compendium containing standards governing product strength, quality and purity. *Id.* The FDA has approved products containing each drug as safe and effective for the uses found in the labeling of the products Generix distributes. The drugs thus meet the well-established test for "general recognition" of safety and effectiveness of 21 U.S.C. § 321(p)(1). *See Weinberger v. Bentex Pharm., Inc.*, 412 U.S. 645, 652 (1973):

> Whether a particular drug is a "new drug" depends in part on the expert knowledge and experience of scientists based on controlled clinical experimentation and backed by substantial support in the scientific literature.

A drug that is "generally recognized" as safe and effective may yet be a "new drug" if it has not been marketed to a material extent or for a material time. 21 U.S.C. § 321(p)(2). Each of the drugs at issue in this case has been widely marketed for years, and therefore satisfies that criterion for exclusion from the "new drug" definition.

B. The "New Drug" Definition Applies To Active Ingredients, Not To Specific Products Containing Those Ingredients.

Because all of the drugs which were the subject of the injunction are generally recognized as safe and effective, they are outside the scope of the "new drug" definition and do not require approval of NDAs as a condition of marketing. The Government nevertheless claims that Generix' products containing those drugs are "new drugs" based on its view that the "new drug" definition applies to individual products. The Government's interpretation of the "new drug" definition

is wrong. Section 321(p) applies to the active ingredient in a product, not to the product.

1. *The statute makes clear that the term "new drug" applies to active ingredients. Alternatively, the statute is ambiguous.* A "new drug" is defined as:

> (1) Any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . ; or
>
> (2) Any drug . . . the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

21 U.S.C. § 321(p).

By including subsection (2) in the "new drug" definition, Congress plainly intended that active ingredients that begin as "new drugs" would become, after a period of time had elapsed and marketing experience had been acquired, something other than "new drugs." Individual products, however, are incapable of achieving "general recognition," because the factors that bear on the safety and effectiveness of a specific product—manufacturing capability, quality control, the precise manner of formulating the finished dosage form—are not part of the information made known to the medical community in the scientific literature. (R. 222-23).

Indeed, a significant part of such information is a closely guarded trade secret that may not be revealed even by the FDA. *See* 21 U.S.C. § 331(j).[14] Accordingly, the "general recognition" test applies to the active ingredient, not the particular product in which the ingredient is formulated. (R. 222-23).

The FDA's contrary interpretation of the Act would create a product-by-product licensing system in which each product is automatically considered a "new drug" under 21 U.S.C § 321 and therefore subject to premarket approval under 21 U.S.C. § 355. Because the FDA's interpretation would render the "new drug" definition superfluous, it must be rejected under the settled principle of statutory construction that Congress should not be presumed to have enacted unnecessary legislation. Each word in a statute should be given effect. *Reiter v. Sonotone Corp.*, 442 U.S. 330, 339 (1979).[15]

The Government attempts to rebut this argument by claiming that there can be general recognition of specific products on a product-by-product basis. The record belies the Government's claim. Both Generix' expert *and* the Government's expert testified that active

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[14]FDA regulations specifically prohibit public disclosure of certain information in a new drug application, including manufacturing methods and processes, quality control procedures and quantitative and semiquantitative formulas. 21 C.F.R. § 314.14 (g). The disclosure of inactive ingredients in products is also prohibited. *See* 21 C.F.R. § 314.14(e)(5) (only the identity of inactive ingredients previously disclosed may be released).

[15]Other parts of the Act would also be rendered superfluous if the Government's argument were accepted. For example, prescription drugs are defined in 21 U.S.C. § 353(b) (1) (A), (B) and (C) as habit forming drugs, drugs which are not safe for use except under the direction of a physician and drugs which are limited for use under the direction of a physician in their NDAs. If all prescription drugs needed NDAs, parts (A) and (B) would be of no effect.

ingredients, not specific products, achieve general recognition:

> Q: (By Mr. Scarlett)[16] Dr. Palmer, take allopurinol. When experts in drug safety and effectiveness form an opinion about the safety and effectiveness of the drug, does that opinion attach to a particular manufacturer's product or does it attach to the active ingredients? In other words, when you go to a conference or symposium and the big issue is, Does allopurinol mitigate gout?, do you talk about allopurinol or do you talk about a brand-name version of that drug?
>
> A: You talk about allopurinol, per se, but implicit is that the drug is well-manufactured and absorbed. You use the good product.

(T. 66-67).

> Q: Are the studies upon which you relied studies designed to use only the active chemical entity rather than the active entity formulated into a drug product?
>
> A: The nature of most of these publications is such that I don't really have any feelings for the nature of the formulation. . . . There is no information in most of the medical literature that I have examined that tells me anything about the nature of the drug product or the formulation or dosage formula that was used.

(T. 222-23).[17]

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[16]Mr. Scarlett was formerly counsel for Generix. He is now Chief Counsel for the FDA.

[17]The compendia referred to in the Act, like the USP and the NF, never refer to particular products made by specific manufacturers.

The "new drug" definition creates a subcategory within the larger category of "drugs." The term "drug" is defined at 21 U.S.C. § 321(g) as:

> (A) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C) of this paragraph; but does not include devices or their components, parts, or accessories.[18]

The Government claims that this definition, particularly subsections (A) and (B), refers unequivocally to products rather than active ingredients. This claim does not withstand analysis. The word "article" is not used in its generic dictionary sense in the statute, i.e., one of a group of things. It is a term of art. The compendia use the term "articles" to refer to those items which are the subjects of monographs in the

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[18]The Government chides the Fifth Circuit for "ignoring the literal language of the statutory definition. . .". (GB. 17). The Fifth Circuit did not ignore the definition. The Government did. It made only passing reference to the definition in its Fifth Circuit brief:

> The definition of "drug" in 21 U.S.C. 321 (g) (1) encompasses drug products.

Government's Fifth Circuit brief at 22 (footnote containing statutory definition omitted).

compendia.[19] Drug substances are the subjects of monographs. Individual products with product-specific differences are not.

The Fifth Circuit stated in its opinion:

> The record shows that the drugs listed in the sources described in subsection (A) of § 321 (g) (1) are "drug substances," not drug products.

654 F.2d at 1116. The Government claims that "there is nothing to that effect in the record." (GB. 17). There is:

> Q: (By Mr. Scarlett): Dr. Smith, could you please explain the basic purpose of the standards that are found in compendia?
>
> A: Yes. When the Pharmacopeia and National Formulary, when they were organized and came into being, *the purpose was to identify for the medical community those major drug substances which they felt were worthy of calling attention to the medical community* because they are suitable for use in treatment of diseases.

(T. 216). Some compendia, like the 1980 NF, only contain monographs on drug substances. Others include drug substances and items other than drug substances. However, none includes individual products. For example, the 1935 USP contained "monographs" on drug substances. In addition, it contained monographs on "official preparations," which were specific combinations of specific ingredients. Binders, coaters and other excipients were not an essential part of the monographs on official preparations:

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[19]This definition actually appears in the 1980 USP. 1980 USP at 2. It does not appear in the 1935 USP which Congress had before it when it passed the Act although the word was used there in the same sense.

> In the case of official *pills* and *troches* a coating may be applied, provided the coating will disintegrate in the alimentary tract and is composed of harmless ingredients; also other suitable diluents or excipients, standardized in the Pharmacopoeia, may replace those directed for official pills and troches, provided they do not alter rates of absorption or other pharmacological behavior.

1935 USP at 1 (emphasis in USP).

The reason the 1935 USP did not include as part of a monograph binders, coaters or other excipients is explained in part by the state of the pharmaceutical art at that time. Many, if not most, of the drug products which were dispensed in this country were fabricated by neighborhood pharmacists, not by industrial manufacturers. The USP allowed the pharmacist latitude in producing the finished product. It is extremely unlikely that Congress intended to require each pharmacist to receive premarket clearance before selling a pill or elixir which contained a different coating or excipient than that contained in a pill or elixir sold by the pharmacist down the block.

Therefore, it is clear that "articles" recognized in the compendia included "drug substances." And, if certain compendia are examined, it might include "official preparations." However, "articles" in the compendia does not include individual products with product specific differences relating to coaters, binders and other excipients.[20]

[20]Later versions of the USP, like the 1980 edition, contain monographs on drug substances and dosage forms. "Dosage form" is defined as "the finished, or partially finished . . . preparation or product of one or more official substances formulated for use on or for the patient." 1980 USP at 2. But even in the 1980 USP, the

The Government's claim that "articles" as used in subsection (B) means something different than "articles" as used in subsection (A) is incorrect. As stated above, "article" is used in the Act as a word of art. It refers to an item which is or might be the subject of a monograph. Since "articles" as used in subsection (A) does not include specific products, "articles" as used in subsection (B) should be given a similar interpretation under the "familiar principle of statutory construction that words grouped in a list should be given related meaning." *Third Nat'l Bank in Nashville v. Impac Ltd., Inc.*, 432 U.S. 312, 322 (1977).[21]

Even if the definition could be stretched to accommodate the Government's argument, it should not be. Statutes should be interpreted to avoid untenable distinctions and unreasonable results wherever possible. *American Tobacco Co. v. Patterson*, 102 S.Ct. 1534, 1538 (1982). The definition of drug does not draw a distinction between prescription and non-prescription drugs. It does not draw a distinction between furosemide and Alka-Seltzer. Yet if the Government's argument is accepted, any sodium bicarbonate product would require approval of an NDA.

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monographs do not describe products. Binders, coaters and other excipients are not listed. For example, the monograph on furosemide tablets states "Furosemide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of [the chemical formula for furosemide]." 1980 USP at 344.

[21]This construction does not render subsection (B) superfluous. That subsection applies to "articles" which might be the subject of a monograph in a compendia but which have been deleted or not yet added. For example, the 1980 USP has 200 more monographs than were contained in the previous edition. 1980 USP at xxxiv. The substances described in these monographs would nevertheless have been "articles" before they were included in the USP and therefore subject to subsection (B). But, since individual products are not the subject of monographs, they are not "articles."

2. *Congress clearly intended that generic products are not "new drugs."* Although any inquiry into a statute's meaning must begin with an examination of its words, it should not necessarily end there. Where the language of a statute is ambiguous or susceptible of at least two plausible interpretations, statutory construction aids, including reference to legislative history, should be employed in determining the statute's meaning. *Weinberger v. Rossi*, 102 S.Ct. 1510 (1982); *Dawson Chemical Co. v. Rohm and Haas Co.*, 448 U.S. 176, 187 (1980); *Ernst & Ernst v. Hochfelder*, 425 U.S. 185, 201 (1976).[22] An interpretation of a statute which arguably might be within the letter of the statute should be rejected if it is not within the spirit or intention of its makers. *United Steelworkers of America v. Weber*, 443 U.S. 193, 201 (1979). Examination of the legislative history supports Generix' position that generics do not require premarket clearance.

The Government is correct in stating that before 1938, the Act did not contain premarket clearance provisions. The rest of its statement on the legislative history is incomplete and misleading.

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[22]One of the FDA's attorneys in this case has recognized that the statutory definition of "drug" is, at best, ambiguous.

> The "new drug" definition in the 1938 Act was ambiguous because it could be read to denote either the generic name for an active ingredient or a "drug product," that is, a particular combination of active and inactive ingredients.

Beers, *Lannett and its Fractious Progeny: Generix, Premo, and the Legal Status of Unapproved Generic Copies of FDA-Approved Drugs*, 70 GEORGETOWN L.J. 173, 180 (1981). Even if the words in the statute favored the Government's interpretation upon superficial examination, it would still be proper to examine the legislative history. *Train v. Colorado Public Interest Research Group*, 426 U.S. 1, 9-10 (1976).

Numerous early drafts of the Act prepared during the 1930's did not provide for premarket clearance. One very vocal member of Congress, Hon. John M. Coffee, believed that these efforts were misguided. He introduced his own bill, H.R. 5286, 75th Cong., 1st Sess., 81 CONG. REC. 1830 (1937). Mr. Coffee said of his proposal:

> Under my bill every manufacturer of a proprietary product must register his formula, file a statement of all claims to be made for it, and the name of the licensed pharmacist or chemist under whose supervision the product is manufactured. Thus a product harmful to health would be prevented from ever reaching the market, since a certificate of registration would be denied if the product contained dangerous ingredients.

81 CONG. REC. A1857 (1937) (remarks of Rep. Coffee).[23] Mr. Coffee's requests for any form of premarket clearance fell on deaf ears until the later part of 1937, when the elixir sulfanilamide incident occurred.[24]

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[23]The Government relegates Mr. Coffee's efforts to a footnote and suggests that the licensing provision was intended to refer to licensing of factories. (GB. 37, n.46). It clearly was not.

[24]Contrary to the Government's claim, diethylene glycol was recognized by Congress at the time as being antifreeze, a far from inactive ingredient. 83 CONG. REC. 7784 (1938) (remarks of Rep. Coffee). The Government's repeated reliance on this incident as supporting its position is misplaced. The Fifth Circuit's holding was carefully limited to inactive ingredients. "Inactive" means inert. An ingredient like diethylene glycol which is lethal is simply not an inactive ingredient even if it is used as a solvent. The Government has never claimed that the binders, coaters and other excipients in Generix' products have a direct effect on

In November 1937, the Senate and the House passed resolutions requesting the Department of Agriculture to transmit to them a full report of the incident. S. Res. 194, 75th Cong., 2d Sess., 82 CONG. REC. 25 (1937); H.R. Res. 352, 76th Cong., 2d Sess., 82 CONG. REC. 134 (1937). A report from the Secretary of Agriculture followed. S. DOC. NO. 124, 75th Cong., 2d Sess. (1937). In his message, the Secretary made recommendations for corrective legislation:

> To protect the public from drugs which, like the "elixir," are dangerous because of their inherent toxicity, it is the Department's recommendation that legislation be enacted to produce at least the following:
>
> 1. License control of new drugs to insure that they will not be generally distributed until experimental and clinical tests have shown them to be safe for use.

Id. at 9-10. Senate Bill 5, 74th Cong., 2d Sess. (1936), the bill which was ultimately passed, was reintroduced with new premarket clearance provisions shortly thereafter. 83 CONG. REC. 5465 (1938). In contrast to bills like Representative Coffee's, which clearly contained licensing provisions for each new proprietary product, S. 5 was not intended to require each manufacturer of each new product to secure premarket approval:

> Section 505(a) requires new drugs to be adequately tested before they are *commercialized.* In order to insure that the

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patients, but only that possible differences in binders, coaters and other excipients may cause differences in the bioavailability and bioequivalence of the active ingredients. If the excipients had a direct and harmful effect, they would necessarily be active ingredients.

> tests made have been complete, the introduction of a new drug in interstate commerce is prohibited unless the manufacturer has submitted full information showing that the drug has been adequately tested and has not been found to be unsafe for use under the conditions prescribed in the labeling. This is not a license provision, but is intended merely to prevent the premature marketing of new drugs not properly tested for safety.

H.R. REP. NO. 2139, 75th Cong., 3d Sess. 9 (1938).

In the same report, the Committee clearly stated that the adulteration provisions of the Act were being rewritten to deal with problems relating to the strength of drugs:

> Section 501 defines adulterated drugs and devices.
>
> * * *
>
> In its requirements for drugs this section tightens up the provisions of existing law by imposing first, reasonable sanitary requirements. It then improves the provisions of the existing law relating to pharmacopoeial and formulary drugs by authorizing variations in strength only, whereas the present law authorizes also variations in quality and purity.
>
> Other provisions close the loophole in the present law under which overstrength drugs, however dangerous, are not subject to regulation.

Id. at 6-7.

In remarking on S. 5, Representative Coffee, the apparent Ralph Nader of his time, noted:

S. 5 does not provide sufficient protection against the repetition of such tragedies as that which occurred last fall, when a so-called elixir of sulfanilamide, a new and untried product, killed almost 100 people in the course of a few weeks. Almost everyone is acquainted with the wholesale poisoning of men, women and children caused by this product which was rushed on the market by a manufacturer so eager for profits that he did not trouble to carry out the few animal experiments needed to show the lethal properties of his "remedy."

At the time of this tragedy Secretary Wallace made excellent recommendations as to the minimum requirements of legislation which should be enacted to prevent the public thus becoming the prey of criminally careless or ignorant manufacturers. These recommendations have been followed but in part. For example, he recommended that license control should be established not only over drugs which might be classified as new in the strictest definition of the term but also combinations of well-known drugs which have not become generally recognized as safe, and well-known drug substances and drug combinations, the labels of which recommend doses larger or more frequent or over a longer period than has become generally recognized as safe.

Secretary Wallace stated the case for licensing the manufacturers of potentially harmful drugs briefly and well. . . .

But despite the great need for licensing at least those manufacturers of the type of

preparations designated by the Secretary, no such control is provided by S. 5. S. 5 does provide licensing control of a sort for those drugs which can be termed new in the strictest sense of the word, but the licensing provision has serious defects.

* * *

The more progressive and forthright members of even the food and patent-medicine industries have admitted that the existing law does not provide the consuming public adequate protection. To replace it with a law which fails to incorporate most of the measures for which consumers and consumer groups have been fighting for the past 5 years, is unthinkable. It would represent a gross betrayal of consumer interests—a betrayal which the citizens of this Nation would not soon forget.

All public-minded Members of Congress should cast their votes against S. 5 and pledge themselves to support a food and drugs bill such as H. R. 5286, the Consumers' Union bill, introduced by myself, which would give the public protection it so urgently needs. *S. 5 would but perpetuate the vicious situation now existing under the present bill,* which penalizes the manufacturers of harmful preparations after injury, often of an irreparable nature, has been done; and frequently does nothing to interfere with their further sale. *A licensing system for proprietary preparations such as that set up by H. R. 5286 would prevent harmful products from ever reaching the market. It would simplify the whole procedure of enforcement and would*

place the burden of the cost, not upon consumers, but upon those manufacturers whose ruthlessness has made it necessary to safeguard the public.

83 CONG. REC. 2279, 2281 (1938) (remarks of Rep. Coffee).

The later conference report on S. 5 reflected Representative Coffee's opinion of what the bill meant. There is no mention of product-by-product licensing. Instead, differences in strength, quality and purity were to be dealt with through the Act's adulteration provisions:

> *Variations in strength, quality and purity of official drugs.* — The House amendment defined drugs recognized in official compendia as adulterated if they differ in strength, quality, or purity from the official standard, but permitted difference in strength on condition that the difference from the standard be plainly stated on the label. The conference agreement permits, on the same condition, differences also in quality and purity.
>
> *Identity of drugs.* — Under the House amendment a drug or device which does not purport to be and is not represented as a drug recognized in an official compendium is considered adulterated if its identity differs from that which it purports or is represented to possess. This provision is omitted under the conference agreement as surplusage since in the case of these drugs and devices, as well as in the case of drugs recognized in an official compendium, if the identity differs from that which it purports or is represented to possess, they would either

be considered to be adulterated under section 501(d) or misbranded under section 502, or both.

H.R. REP. NO. 2716, 75th Cong., 3d Sess. 24 (1938) (statement of House conferees) (emphasis in report).[25]

This legislative history shows conclusively that although Congress adopted a limited premarket clearance system as a response to the elixir sulfanilamide incident, that system fell far short of the product-by-product premarket clearance that some Congressmen wanted in 1938 and which the FDA wants now.

Any doubt about Congress' original intent is dispelled by an examination of the legislative history of the 1962 amendments to the Act. Congress' paramount concern at that time was the excessive cost of prescription drugs. [1962] U.S. CODE CONG. & AD. NEWS 2884-2936. The legislation's primary goal was to reduce prices.

The legislation originated as the result of an investigation conducted by the Senate Subcommittee

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[25]The adulteration provisions in § 501, now 21 U.S.C. § 351, read in part:

> A drug or device shall be deemed to be adulterated—
>
> * * *
>
> (b) If it purports to be or is represented as a drug the name of which is recognized in an official compendium, and *its strength differs from, or its quality or purity falls below, the standard set forth in such compendium.*
>
> * * *
>
> (c) If it is not subject to the provisions of paragraph (b) of this section and its strength differs from, or its purity or quality falls below, that which it purports or is represented to possess.
>
> (d) If it is a drug and any substance has been (1) mixed or packed therewith so as to reduce its quality or strength or (2) substituted wholly or in part therefor.

on Antitrust and Monopoly. The subcommittee found that the major drug companies made apparently unconscionable profits:

> These "extraordinary margins and profits" were attributed to the "tight control of the market in the hands of a few large companies" which resulted in rigid price structures over long periods of time. The subcommittee found that one of the principal factors underlying this market control was the success of major drug companies in persuading physicians to prescribe drugs by the companies' trade names despite the existence of less expensive, chemically identical generic-named drugs.

Note, *Drug Amendments of 1962 — Generic Name Prescribing: Drug Price Panacea*, 16 STAN. L. REV. 649, 651-52 (1963-64). The legislation was specifically designed to encourage generic-name prescribing and lower prices.

> The impetus for generic-name prescribing was to be created by provisions (1) assuring physicians that any drug sold in the United States, whether made by a large well-known manufacturer or a small, obscure one and whether sold by trade or generic name, would be of adequate and acceptable quality and (2) simplifying generic names and bringing them to the physician's attention.

Id.

Three specific sections of the legislation were to insure the quality of prescription drugs.

> The first requires that every "establishment in any State engaged in the manufacture,

> preparation, propagation, compounding, or processing of a drug or drugs" register with the Secretary of Health, Education and Welfare. . . . The second section requires the FDA to inspect every establishment registered with the Secretary at least once every two years. . . . The third section requires adequate manufacturing safeguards and allows the FDA to seize drugs which have been manufactured without adequate safeguards even though their essential characteristics are unimpeachable.

Id. at 654-55. As stated in S. REP. NO. 1744, 87th Cong., 2d Sess., *reprinted in* [1962] U.S. CODE CONG. & AD. NEWS 2884, 2890:

> Section 5 of the bill, as amended, is intended to give the Food and Drug Administration additional authority to require that sound methods, facilities, and controls be used in all phases of drug manufacture and distribution. By an amendment of section 501(a)(2) of the Food, Drug, and Cosmetic Act, a drug would be deemed to be "adulterated" if such methods, facilities or controls were found not to conform to current good manufacturing practice to assure safety, identity, strength, quality and purity of the product.
>
> * * *
>
> This section, together with the registration and factory inspection provisions of sections 3 and 4 of this amended bill, would greatly increase the Food and Drug Administration's authority over drug manufacture and distribution. These provisions should prove helpful in reaching persons who are responsible for putting drugs

of questionable or unknown quality on the market.

The import of this history is clear. Congress intended to provide a mechanism by which the FDA had greater control over the formulation of generic drug products. But the mechanism was the adulteration provisions of the statute, not the NDA requirement.

Again and again, Congress indicated its intent that generic products should be used to a greater degree and that the means for encouraging such use were the factory registration, inspection and adulteration provisions of the statute, not the NDA requirement:

> MR. HART: One of the purposes of the bill is to bring about conditions under which doctors may prescribe drugs by generic name and be confident that drugs meeting the highest standard are supplied.
>
> At the root of this whole problem is the fact that certain drugs have achieved acceptance by their trade names in the mind of the physician who writes the prescription. That acceptance has been won through the efforts of the industry's salesmen, who are called detail men; it has been won by sustained and expensive and, why blink at the unhappy fact, sometimes misleading advertising; and, finally, that acceptance flows from the weakness of the law which makes it possible for a few unqualified manufacturers to operate.
>
> * * *
>
> It is most unfortunate that high prices in prescription drugs should result from the fact that many doctors are uneasy about prescribing by generic names. Why is this so? The answer

is that it is the weakness of the law which makes for this insecurity and makes high prices inevitable for prescription drugs.

* * *

The stricter standards for inspection imposed by this bill, and its requirement for registration, will guarantee the quality of every drug sold in the United States. The physician will know it is of adequate and acceptable quality whether it is marketed under a brand name or under a generic name.

MR. KEFAUVER. Mr. President, will the Senator yield?

MR. HART. Gladly.

MR. KEFAUVER. The Senator conducted this important part of the hearings. Is it not true that the drug manufacturers spent $5,000 a year per physician to send out detail men who provide the physician with sample drugs and give him information about their own drugs, and for other selling and promotional expenses?

MR. HART. That was indicated from our record of the hearings.

MR. KEFAUVER. Is not the principal purpose of detailing to impress on the mind of the physicians a trade name and to leave the impression that if they used a drug with a trade name of a well-known manufacturer, they were perhaps getting a purer drug or a better drug or a more efficacious drug than would be so if the drug had been purchased by the generic name at a lower price?

MR. HART. The testimony indicated clearly that that was the purpose of detailmen, and that was, in fact, the way they performed.

MR. KEFAUVER. *While the provision of the bill which the Senator is talking about now, relating to stricter factory inspections and control measures, may not be as effective as licensing, it will, in the first instance, be effective and give the physician adequate grounds for relying upon the soundness, purity, strength, and efficacy of any drug purchased or manufactured in this country, whether prescribed by the generic name or by the trade name. Is that correct?*

MR. HART. I feel that is so. Certainly it is our hope.

Let us not churn up the water now over the dam. Let us be thankful that we have a bill before us which will give assurance to physicians that if they prescribe generically the sources from which the drugs will be secured will be inspected, so that standards will be met. I think this is a most important aspect of the proposed legislation which, in the excitement and emotions following the incidents with respect to thalidomide, has been overlooked.

108 CONG. REC. S17,381-82 (1962).

The Government and amici curiae attempt to muster support for their position by citing irrelevant and out-of-context parts of the legislative history. For example, the Government relies on the following statement by Senator Kefauver:

> Hence the requirement of this bill that the Food and Drug Administration pass on the efficacy as well as the safety of new drugs should make it more difficult to contend successfully that there is a difference between two brands which are identical generically and both cleared as to safety and efficacy.

106 CONG. REC. 12,665 (1960). However, the bill he was discussing contained product licensing provisions which were not incorporated into the amendments which were passed. They provided:

> Licenses . . . may be issued only upon a showing that the establishment and the products for which a license is desired meet standards, designed to insure the continued chemical structure, strengthening, quality, purity, and safety, and efficacy of such products, prescribed by regulations, . . .

S. 3677, 86th Cong., 2d Sess. 4 (1960). Another oft-cited portion, which is emphasized, is taken out of context:

> The term "new drug" is presently defined as one not generally recognized to be safe for the claimed uses or one, which while so recognized, has not been used for a material time or to a material extent for such uses. The bill would expand this definition so that the term "new drug" would also include one not generally recognized to be effective for the claimed uses or one, which while so recognized, has not been used for a material time or to a material extent for such uses. *Thus, every brand new product, and every new claim for an existing product, would be subject to the tests and*

> *procedures established in section 505 of the act.*

108 CONG. REC. 17,366 (1962). It is apparent that this statement applies to the new effectiveness provisions in the 1962 amendments and not to generic products. Moreover, as the Fifth Circuit noted:

> Isolated references in the legislative history can not overcome the plain language and override logic of the Act.

654 F.2d at 1118, n.5.

Finally, in the late 1970's, in light of decisions like *United States v. Articles of Drug . . . Lannett*, 585 F.2d 575 (3d Cir. 1978), Congress specifically was asked to adopt the very system which the FDA wanted. *E.g.*, S. 1075, 96th Cong., 1st Sess. (1979). Congress was placed on notice that different courts had adopted different interpretations of the Act on the precise issue raised here. The Senate Report accompanying that bill, S. REP. NO. 96-321, 96th Cong., 1st Sess. 60 (1979) [the Report] stated:

> Section 118 amends section 505(a) by making it clear that with three exceptions, every person marketing a drug must submit a new drug application (NDA) to FDA and have that application approved. Current law's provision governing the submission of an NDA, section 505(a), has been interpreted by at least one Federal Circuit Court to exempt the manufacturer of a generic drug from even notifying FDA that it is marketing a drug product.

The proposed legislation would have legitimized many of the FDA's current practices. It would have eliminated the "new drug" concept:

> S. 1075 would . . . [eliminate] the concept of "new drug" and, together with other provisions, establish a single regulatory system for all drugs marketed in the United States. The effect of this provision, together with amendments to the drug approval process, is to make all drugs, with certain narrowly defined exceptions, subject to the approval process and the concomitant regulatory controls.

Report at 14. It would have "expand[ed] the factors considered by the FDA in determining whether the methods used in . . . the manufacture of a drug are adequate by adding as new factors a drug's stability and bioavailability." Report at 16. It would have allowed the FDA to use an "abbreviated approval procedure for generic versions of a drug that has been approved under the Act for at least 7 years . . .". Report at 16. It would have distinguished between prescription and OTC drugs. Report at 19. And it would have continued to allow the marketing of OTC drugs if they were found to be generally recognized as safe and effective and not misbranded. Report at 19. These points are illustrative rather than exhaustive.

The members of the Senate who prepared the report were well aware that prior legislation had not been interpreted uniformly by the courts. Congress was given an opportunity to accept with great specificity the FDA's concept of an ideal premarket clearance system. This Congress refused to do.

Although Congress' rejection of the proposed legislation, standing alone, is not determinative of the issue here, it is an additional piece of information to be considered in conjunction with the words of the statute, the contemporaneous legislative history, other case law and the FDA's interpretation of the Act for over 30

years. *Federal Trade Commission v. Bunte Bros.*, 312 U.S. 349 (1941); *Canada Packers, Ltd. v. Atchison, Topeka and Santa Fe Railway Co.*, 385 U.S. 182 (1966); *Administrator, Aviation Administration v. Robertson*, 422 U.S. 255 (1975).

3. *The FDA has consistently interpreted "new drug" as relating to active ingredients, not to specific products.* The FDA had no doubt what the statute meant for almost 40 years. Beginning shortly after the Act's enactment in 1938, the FDA concluded that a product with the same active ingredients as one already approved by the agency was not a "new drug" under 21 U.S.C. § 321(p) and therefore could be marketed without prior FDA approval under 21 U.S.C. § 355.[28] Accordingly, the FDA commenced the practice of issuing "not new drug" opinions:

> [By] 1968 the Food and Drug Administration had issued several thousand letters and oral determinations to drug manufacturers stating

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[28] *Conditions for Marketing Human Prescription Drugs*, 40 FED. REG. 26,142, 26,143 (1975). (R. 160-75). The preamble to this proposed rule contains the only integrated history of the FDA's interpretation of the term "new drug." The Government has argued that its decision to permit marketing of drugs without NDAs was due to "war-related staff shortages." This may have been a factor, but the FDA's Annual Report covering that period does not mention it. Instead, it refers to "the revision in policy as to what constitutes a new drug" and "the effect of the war on the development and marketing of new-drug products." [1942-1943] FDA ANN. REP. at 47. (R. 176-79). The Federal Register document merely confirms that the agency's practice, which continued for more than 30 years, was based on a considered judgment that a product with the same active ingredients as one for which an NDA was already approved was not a "new drug" as a matter of legal interpretation. It ill behooves the Government to call Generix' position absurd in light of prior FDA practice. (GB. 14, n.9).

> that various types of drugs were no longer covered by the definition of new drug in section 201(p) of the act in that they had become generally recognized as safe and effective and had been used to a material extent or for a material time, and thus that they had achieved "old drug" ("not new drug") status. Under the statute, an old drug need not be the subject of an effective or approved NDA prior to marketing.

40 FED. REG. 26,144. No mention is made in this account of any FDA belief that product-specific factors such as inactive ingredients, bioavailability and manufacturing procedures were relevant to the decision to issue "not new drug" opinions. Indeed, since consideration of those factors would have precluded a finding that a drug was "generally recognized" as safe and effective, it follows that from shortly after passage of the Act until 1968, the FDA viewed the "new drug" definition as applying only to active ingredients, not to specific products.

Deference should be accorded to the interpretation given a statute by the agency charged with its administration. *Udall v. Tallman*, 380 U.S. 1, 16 (1965). Moreover, contemporaneous construction of a statute gains particular weight when made "by the men charged with the responsibility of setting its machinery in motion, of making the parts work efficiently and smoothly while they are yet untried and new." *Norwegian Products Co. v. United States*, 288 U.S. 294, 315 (1933).[27] *See also Andrus v. Shell Oil Co.*, 446 U.S. 657, 667-68 (1980).

[27]The FDA's interpretation continued well beyond the 1962 amendments. The Government has implied that the 1962 amendments prompted a change in the FDA's interpretation of the "new drug" definition. This view is belied by the cited Federal Register account

It was not until 1968 that the FDA abandoned the policy of issuing "not new drug" opinion letters. 40 FED. REG. 26,143. Even then, however, the FDA did not modify its interpretation of the "new drug" definition:

> [T]he agency fully realized that it would not be feasible from an administrative standpoint, or necessary for protection of the public health, *or consistent with the definition of new drug in section 201(p) of the act to require either a full or an abbreviated NDA for all human prescription drugs.*

40 FED. REG. 26,144. At about that time, the FDA commenced the practice of approving what is known as an "abbreviated NDA," or ANDA, to regulate products whose active ingredients' safety and effectiveness are well-established. An ANDA is an NDA that does not include safety and effectiveness data on a product's active ingredient, but does include product-specific information, such as bioavailability and manufacturing data.

The ANDA is a regulatory hybrid whose legal validity has never been established. The FDA concedes

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and by the following excerpt from a 1963 letter from John F. Palmer, Chief of the FDA's New Drug Status Branch, Division of New Drugs:

> However, new manufacturers desiring to market an article no longer regarded as a new drug would not be required to submit new drug applications, although they would, of course, have to comply with all pertinent requirements of the Act and regulations relating to adulteration and misbranding including, as an example, the "current good manufacturing practice" regulations.

Letter from John F. Palmer to Lennart Lindberg (drug company executive) (Oct. 2, 1962). (R. 180-85).

that products for which it requests an ANDA are "generally recognized as safe and effective":

> If one analyzes the notice [permitting the filing of an ANDA], it implies that the generic drug is generally recognized as safe and effective, and hence is not a new drug because no additional safety and effectiveness data need be submitted in the ANDA.

McEniry, *Drug Monographs*, 29 FOOD DRUG COS. L.J. 166 (1974) (Ms. McEniry, a lawyer, was Assistant Director of Regulatory Affairs for the FDA's Bureau of Drugs).

Obviously, if a product is not a "new drug," no NDA, abbreviated or otherwise, may legally be required by the FDA. In fact, the ANDA system has achieved a certain grudging toleration by the drug industry.[28] To avoid a confrontation, most companies will comply with the FDA's demands regardless of their skepticism about the validity of what the agency wishes them to do. It is nevertheless a fact that the FDA's insistence on ANDAs for products that are not "new drugs" has no basis in law.

Any doubt that the FDA itself does not regard the "new drug" definition as applying to specific products is removed when one examines the agency's approach to OTC products. The new drug definition at 21 U.S.C. § 321(p) does not distinguish between prescription products and OTC products. Yet the FDA has established regulations under which OTC products are classified as "generally recognized" as safe and effective, and can

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[28]Toleration of the ANDA system, as well as the FDA's approach to OTC drugs, is exemplified by the amici curiae briefs filed on behalf of the Generic Pharmaceutical Industry Association and the Proprietary Association.

be marketed without NDA approval, if they meet the standards applicable to categories of OTC products (such as analgesics and laxatives). *See* 21 C.F.R. § 330.10. If the "new drug" definition applies to specific products, the agency's approach to OTC drugs is illegal. The regulations developed for OTC drugs are not based on information relating to specific products, such as bioavailability, inactive ingredients and manufacturing procedures. Instead, OTC drug products are considered by the FDA to be outside the "new drug" definition as long as the products contain only approved active ingredients, are manufactured in accordance with the current good manufacturing practices, are properly labeled, and contain "suitable" inactive ingredients. *See* 21 C.F.R. § 330.1.

The FDA has never been able to reconcile its diametrically opposed systems for OTC and prescription products in legal or theoretical terms. Rather, the agency insists that because prescription products are more powerful and are used in more serious conditions, their manufacture requires closer supervision. But those factors are irrelevant to the proper application of the "new drug" concept, which relates to the safety and effectiveness of *all* active ingredients, whether they are incorporated in prescription or OTC products. The FDA's more relaxed approach to OTC products demonstrates that the agency's insistence on product-specific approval of prescription products is the result of the FDA's view of what constitutes an administratively convenient system of regulation, and not of an interpretation of the law as it was written by Congress.

4. *This Court's decisions suggest that "general recognition" relates to the active ingredients in a drug product.* This Court has recognized that drug safety

and effectiveness determinations apply to active ingredients, not to specific products. In *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973), this Court held that when the FDA withdraws approval of an NDA for a product, known as a "pioneer," the underlying effectiveness determination applies to "me-too" products, i.e., products marketed without an NDA in reliance on the FDA's approval of the "pioneer." This Court noted:

> paralysis would result if case-by-case battles in the court were the only way to protect the public against unsafe and ineffective drugs. Moreover, if every "me-too" drug in a particular general category had to be put to the test in court actions, great inequities might well result.

412 U.S. at 626. This holding, regarded as one of the FDA's most significant victories in the agency's effort to enforce the new drug provisions of the Act, would have been completely unnecessary if, as the FDA contends, the "new drug" definition applies to product-specific formulations of active ingredients. Information on the safety of specific products is incapable of attaining "general recognition" status, and therefore specific "me-too" products would have been illegally on the market. *See also Weinberger v. Bentex Pharm., Inc.*, 412 U.S. 645 (1973).

The Government's argument, if accepted by this Court, would not only render decisions like *Hynson* and *Bentex* unnecessary. It would also lead to the conclusion that they were decided incorrectly. If, as the Government claims, product-specific considerations relating to bioavailability and bioequivalence are significant in determining whether an NDA should be approved, they would also be relevant in determining

whether NDA approval should be withdrawn. If a pioneer product were taken off the market because it failed tests relating to bioavailability and bioequivalence, generic copies of the pioneer with no bioavailability or bioequivalence problems should not necessarily suffer the same fate as the pioneer. Yet this Court has reached the contrary conclusion.

C. The Government's Interpretation of "New Drug" As Applying to Specific Products Should Be Rejected By This Court.

The Government presents several arguments why the "new drug" definition should be applied to specific products rather than their active ingredients. None of those reasons withstands analysis.

Citing this Court's decision in *Weinberger v. Bentex Pharm., Inc., supra*, the Government argues that a harmonious reading of the "new drug" definition at 21 U.S.C. § 321(p) with the "new drug" approval provision at 21 U.S.C. § 355 requires that both sections be exactly equal in content. This Court stated that "the reach of scientific inquiry under both" provisions "is precisely the same." 412 U.S. at 652. According to the Government, this statement means that a product cannot be "generally recognized" as safe and effective unless all of the information required for approval of an NDA meets the "general recognition" test. The Government's interpretation is necessarily incorrect, however, because it would require that *all* products be considered "new drugs."

The Government's argument construes the *Bentex* decision more broadly than this Court intended. This Court was faced with an argument that an active ingredient lacking substantial evidence of effectiveness

in the form of adequate and well-controlled investigations, the criterion for approval of an NDA for a specific product under § 355, could nevertheless be "generally recognized as effective" under the "new drug" definition, and therefore immune from FDA regulation as a "new drug."

The purpose of adequate and well-controlled investigations is to demonstrate the effectiveness of a product's active ingredient, not of any particular formulation of that active ingredient. This Court properly concluded that an active ingredient should be subject to the same effectiveness standard both with respect to the jurisdictional question of "new drug" and for purposes of NDA approval. This Court was not presented with the issue of whether § 321(p) applies to the formulation of each specific product.

The FDA itself does not interpret *Bentex* in the manner it urges here. It does not, for example, require "substantial evidence of effectiveness" in the form of "adequate and well-controlled investigations" as a condition for approving ANDAs. (R. 31). If § 321(p) applied to *products*, and if the scope of the inquiry were literally the same under that section and under § 355, which *does* apply to products, *USV Pharm. Co. v. Weinberger*, 412 U.S. 664, 665 (1973), then approval for each product should require a full NDA including adequate and well-controlled investigations of the safety and effectiveness of the specific *product* for which approval is sought. But the FDA imposes no such requirement.[29]

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[29]The entire thrust of this case is that the FDA wants this Court to give it regulatory authority to require NDAs for all new drug products. But the FDA cannot oversee NDAs including full safety and effectiveness determinations for all generic and OTC products. Ironically, if this Court gives the FDA the power to require NDAs for all new drug products, the FDA could then be

Although the Government advocates a "harmonious" reading of §§ 321(p) and 355 (R. 46), its interpretation of the way those provisions relate leads to a dissonant result. Under § 355, a manufacturer seeking NDA approval for its product must submit a broad range of highly specific data relating to the materials used in the specific product formulation, and to the "methods used in, and the facilities and controls used for, the manufacturing, processing, and packing" of the product. 21 U.S.C. § 355(d)(2)-(4). The FDA's regulations amplify these requirements. *See* 21 C.F.R. § 314.1(c). Having argued that §§ 321(p) and 355 are literally equal in content, the Government made the extraordinary assertion that "this information—which varies from one version of a generic drug to another—must be available to experts generally and form a basis for the general recognition of each product's safety and effectiveness." (R. 47).[30]

This construction of the Act is impossible. The information in an NDA is voluminous; merely to describe it requires six pages of densely-packed type in the Code of Federal Regulations. The information is detailed

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sued by someone and forced to comply with this Court's mandate. The FDA would be in no position to comply. *See Weinberger v. Bentex Pharm., Inc., supra*, 412 U.S. at 652 (approximately 100,000 to 500,000 unapproved OTC products on the market); Final Report, Comm'n on Federal Drug Approval Process 94 (Mar. 31, 1982) (full NDA approval for generics would not have been feasible since there are as many as 13 generics being sold for every pioneer).

[30]The Government has retreated somewhat from this position in this Court and claimed that a product can achieve general recognition because an expert may recognize the brand name in published test results. (GB. 26). This unsubstantiated claim ignores the record evidence that experts are generally familiar only with a product's active ingredient, not with any specific product formulation. (T. 66-67, 222-23). Authoritative volumes like the USP and NF never refer to individual products.

and highly technical, covering such topics as "a description of the physical facilities" used in making a product and "the qualifications, including educational background and experience, of the technical and professional personnel" involved in the manufacturing process, and the "method of preparation of the master formula records and individual batch records and manner in which these records are used." 21 C.F.R. § 314.1(c) (NDA §§ 8a, b and g).[31]

None of this information is capable of being widely known by drug experts. (R. 223). It is, in fact, considered trade secret information under the Act and the FDA's regulations. 21 U.S.C. § 331(j); 21 C.F.R. § 314.14(g). The FDA's position that § 321(p) applies to *products*, and that "general recognition" requires knowledge by scientific experts of all NDA data, leads to the illogical result that there can be no such thing as "general recognition" even though Congress took great care to delineate a category of drugs to which that concept applies.

As a logical matter, "general recognition" can apply only to those attributes that are capable of achieving widespread knowledge among experts. Since experts are likely to be aware of the performance characteristics only of the active ingredient in a product (R. 222-23), it follows that a determination of "new drug" status depends on the acceptance in the scientific community of the safety and effectiveness of the active ingredient.

The Government also asserted that courts should give deference to the FDA's interpretation of the Act. (R. 47-48). Such deference should not be accorded to an interpretation which is at odds with the plain meaning of the Act and with the FDA's own contrary interpretation,

[31]These are but three of 17 subsections in one section of the NDA. The NDA contains 12 sections in all. The NDA itself usually occupies entire filing cabinets.

applied since 1938 and stated as recently as 1977. Courts need not defer to an administrative construction of a statute when there are compelling indications that it is wrong, *Espinoza v. Farah Mfg. Co.*, 414 U.S. 86, 94-95 (1973), or if the interpretation has not been uniform or consistent, *Burnet v. Chicago Portrait Co.*, 285 U.S. 1, 16 (1932); *International Brotherhood of Teamsters v. Daniel*, 439 U.S. 551, 566 (1979).

The Government's third ground for requesting that its interpretation of "new drug" be accepted was that premarket review of all prescription drug products would contribute to achieving the FDA's public health objectives. (R. 48-50). Adoption of the FDA's view of "new drug," according to this argument, would

> assure that each version of a drug will be approved by FDA as safe and effective before marketing. This process will prevent the administration to human beings of drugs that may be, because they are improperly made, extremely dangerous.

(R. 48). However, the FDA is not free to exceed its statutory boundaries and then argue that, because its objective is worthwhile, the boundaries must be expanded to include whatever the agency has decided to do:

> In our anxiety to effectuate the congressional purpose of protecting the public, we must take care not to extend the scope of the statute beyond the point where Congress indicated it would stop.

62 Cases of Jam v. United States, 340 U.S. 593, 600 (1951).

Moreover, the FDA does not lack the regulatory tools needed to assure product quality. The FDA may

invoke the adulteration provisions of 21 U.S.C. § 351 against imperfectly manufactured products. The agency may enforce the current good manufacturing practice regulations at 21 C.F.R. § 211. If the FDA is concerned that a product is not of adequate strength, quality and purity, the Act provides a specific remedy under 21 U.S.C. § 351(b). That section states that a product is adulterated if it is recognized in an official compendium, such as the USP, and fails to meet the compendial standards of strength, quality and purity. Such standards include bioavailability and bioequivalence. If the FDA regards the standards as insufficient, it may request a revision in the compendium, failing which it may issue its own standards. It is therefore specious to argue that the FDA cannot adequately monitor the safety of prescription products unless they are subject to NDAs.[32]

The parade of possible horribles presented by the Government and the amici curiae should be given little if any weight. There is no evidence in this record that any of Generix' products are dangerous. Incidents outside this record, like the indictment of the pharmacist from Ohio, are simply not documented. The pharmacist was acquitted and there is no competent evidence here that the product which he distributed caused his customer's

[32]The Government claims that adherence to compendial standards required by the adulteration provisions does not solve potential problems because "those standards are not designed to assure bioequivalence." (GB. 36, n.44). The Government is wrong. It admits "[d]rugs with similar bioavailability are considered "bioequivalent." (GB. 6, n.9). Bioavailability standards are set forth in the 1980 USP which the Government cites. For example, the monograph on furosemide tablets specifies that they must dissolve within 30 minutes pursuant to the testing procedures on disintegration used in part 701 of the physical testing section of the formulary. Part 701 describes the precise manner in which a tablet must be tested to determine if it disintegrates within the allotted time.

death. Moreover, these unfounded accusations are based on the philosophical premise that courts should ignore statutory language and legislative history and fashion remedies to correct perceived problems. This type of "statutory construction" is improper. *Northwest Airlines v. Transport Workers Union*, 451 U.S. 77 (1981).

Finally, it is far from clear that maximum regulatory control is the ultimate panacea.[33] The most recent drug

[33]Final Report, Comm'n on the Federal Drug Approval Process, (Mar. 31, 1982) [Report], relied on by the Government and various amici curiae, does not lend solid support to their position. Although the Commission, which appears to be dominated by representatives of the major drug companies, consumer groups and the Government, suggested that there should be some form of premarket clearance for generics, it conceded that the FDA was physically incapable of processing NDAs for all generics, that most of the NDA requirements for information about chemistry and manufacturing controls were excessive and adequately dealt with through the good manufacturing practice program and that:

> Perpetuating regulatory requirements for a full NDA for generic products may protect incentives [for brand name manufacturers], but it serves no immediate public health purpose, is not scientifically justifiable, and may lead to unnecessary and ethically questionable human experimentation.

Report at 76-77, 94, 96. It is interesting to note that the USP Advisory Panel to the Commission, a somewhat more independent body, had published an interim report on October 20, 1981 which was much more critical of the stance the FDA had taken in recent years concerning generic products. It pointed to the untoward delays in the processing of paper NDAs and ANDAs for duplicate products. It stated that possible health or safety problems could be handled by compendial standards and CGMP requirements rather than the NDA process. The panel concluded:

> We realize that our recommendations fly in the face of major efforts by FDA in recent years to build up case law supporting FDA controls over premarketing of every strength and every dosage form of *every* drug no matter

incident which caused multiple deaths and injuries involved a brand name product called Selacryn, which was approved by the FDA before it was sold. Selacryn caused more injuries and deaths than have even been alleged to have been caused by unapproved generic copies of brand name products.[34]

The regulatory tilt of government bureaucrats causes them to believe that the free market will not function safely and effectively absent government interference. That assumption is incorrect. One of the reasons underlying Generix' decision to stop selling unapproved generic products may have been its marketing perception that consumers and retailers would not buy them. This concern is shared by other manufacturers and distributors of generics:

> [A] high court decision upholding the 5th Circuit could prove to be a public relations disaster for the generic drug industry. Years have been

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how long similar products have been marketed by other companies or even by the same company. Yet when the total FDA manpower investment required and the cost to both the companies and to FDA are judged against the benefits of faster processing of New Drugs and the cost of improving the compendial-CGMP-inspection process, this appears to our Panel to be a *major* opportunity for FDA to improve its operations overall.

Id. at 3 (emphasis in Report).

[34]The reporters are full of cases involving massive injuries and deaths caused by brand name products approved by the FDA. *See, e.g.*, cases cited in FRUMER & FRIEDMAN, PRODUCTS LIABILITY, §§ 33.01 *et seq.*, Drugs & Druggists (1982); Annot., 70 A.L.R.3d 315 (1976); 94 A.L.R.3d 748 (1979); 94 A.L.R.3d 1080 (1979); 2 A.L.R.4th 1091 (1980). Of course, legal liability was not imposed against the manufacturers in all of these cases. However, plaintiffs were injured and killed.

> spent boosting public confidence in the products, which still seem highly susceptible to damaging publicity – however unmerited – about their safety. A recent ad for an ABC news broadcast suggested that generic drugs could save consumers money, but also cost them their lives. If many generic drugs without premarket clearance were marketed, damaging stories of that ilk no doubt would multiply.

14 Wash. Drug Letter, No. 10 at 2 (Mar. 8, 1982). The free market is more efficient at solving problems, whether real or perceived, than government regulators.

CONCLUSION

The decision of the court of appeals should be affirmed.

Respectfully submitted,

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In the Supreme Court of the United States

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UNITED STATES OF AMERICA, PETITIONER

v.

GENERIX DRUG CORPORATION, ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE ELEVENTH CIRCUIT

REPLY BRIEF FOR THE UNITED STATES

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REPLY BRIEF FOR THE UNITED STATES

INTRODUCTION

Respondents[1] contend that the Federal Food, Drug, and Cosmetic Act allows them to market unapproved, untested and potentially unsafe generic drugs. As we have shown in our main brief, this interpretation of the Act's "new drug" provisions (21 U.S.C. 355) is contrary to the Act's plain language and legislative history, and would pose serious dangers to the public health.

The Act embodies the Congressional determination that in order adequately to protect the public health, the safety and effectiveness of drugs must be established before they

[1]This brief refers to respondents collectively as "Generix." Generix's brief is cited as "Resp. Br." The government's main brief is cited as "Gov't Br."

are marketed. Ignoring this Congressional directive, respondents argue, in effect, that generic drugs should be allowed on the market unless and until FDA is able to prove that they are unsafe or ineffective. The statutory premise of respondents' argument—that the term "new drug" refers only to active ingredients rather than drug products—is based upon an erroneously restrictive reading of the Act's "drug" and "new drug" definitions.

At the center of this case is the statutory mechanism for ensuring that the safety and effectiveness of all drugs marketed in the United States are demonstrated prior to sale. Under the carefully crafted statutory scheme, the assurance that a given drug has been shown to be safe and effective is provided in one of two ways:

a) Drugs that are "new drugs" within the meaning of 21 U.S.C. 321(p) must be approved by the FDA prior to marketing. FDA will not approve the marketing of a drug unless specified safety and effectiveness testing has been performed and that testing shows the drug to be safe and effective for its proposed use. See 21 U.S.C. 355(d).

b) Drugs that are "generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof," 21 U.S.C. 321(p)(1), may escape the premarketing approval requirement. As this Court has made clear, however, such general recognition among experts cannot exist in the absence of the kind of evidence of safety and effectiveness that would be required for approval of a new drug application (NDA) if one were submitted. See *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 629-632 (1973).

Thus, in both classes of drugs the requisite safety and effectiveness testing has been performed prior to marketing: qualified experts (at the FDA for "new drugs" and in the expert community at large where "general recognition" exists) have reviewed that testing and confirmed that it shows the drugs in question to be safe and effective.[2] In either case, the public is protected as Congress intended. The drug products involved in this case, however, have not gone through the FDA approval process and are not generally recognized by experts as safe and effective.

Respondents seek to create an exception to this clear statutory structure that Congress neither expressed nor intended. In their view, if a generic drug has the same active ingredient as a pioneer drug that is itself not a new drug,[3] the generic may be sold without any preclearance, even though its inactive ingredients—which may constitute 90% of an individual product—may differ from those of the pioneer it purports to copy. This interpretation is clearly at odds with the system Congress established. It conflicts with the statutory language, which creates no exemption such as respondents claim. It conflicts with the legislative history by

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[2]As the Eighth Circuit recently held in the context of "new animal drugs," the approval of a new drug application by FDA, which allows a "new drug" to be marketed, is not equivalent to a conclusion that a drug described in the NDA is not a "new drug." *United States* v. *Undetermined Quantities of Various Articles of Drug . . . Equidantin*, 675 F. 2d 994, 1001 (1982), petition for cert. pending, No. 81-2402 (filed July 1, 1982). See also Gov't Br. 25 n.31.

[3]Generix expressly disclaims any reliance on the argument that its drugs are not new drugs because they have the same active ingredients contained in pioneer drugs that have obtained FDA approval (Resp. Br. 11). Instead, Generix contends (*id.* at 11-12) that its products need no FDA approval because their active ingredients are generally recognized as safe and effective. The same argument could have been made for Elixir Sulfanilimide, the drug that caused the tragedy that led to enactment of the new drug provisions in 1938 (see Gov't Br. 27-29).

permitting the sale of prescription drugs that have neither been reviewed by FDA nor received general expert recognition. Finally, it conflicts with the strong public policy underlying the Act: protecting patients from untested and potentially unsafe or ineffective prescription drugs.

I. PREMARKET REVIEW OF GENERIC DRUGS IS NECESSARY TO PROTECT THE PUBLIC

Respondents do not deny that generic drugs can differ from approved "pioneer" drug products in bioavailability, *i.e.*, the amount of the active ingredient that reaches the site of action in the body and the rate at which this occurs (Resp. Br. 6). See *Inwood Laboratories, Inc.* v. *Ives Laboratories, Inc.*, No. 80-2182 (June 1, 1982), slip op. 3 n.5. Nor do they deny that such differences may affect adversely the safety and effectiveness of generic drugs (Resp. Br. 6; J.A. 64-65). In effect, therefore, respondents concede that even if a pioneer drug is safe and effective, generic drugs—such as those Generix marketed—*may* be unsafe (Resp. Br. 4, 6, 10).[4] Some unapproved generics have in fact been found to pose substantial health risks (see Gov't Br. 35 n.42; *SK & F, Co.* v. *Premo Pharmaceutical Laboratories, Inc.*, 625 F. 2d 1055, 1061 n.4 (3d Cir. 1980)).

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[4]Respondents continue to contend that this case is moot (Resp. Br. 9 n.12) for the reasons stated in their earlier suggestion of mootness which this Court rejected on May 3, 1982. Respondents now add that "[c]ounsel has recently been informed that the United States Marshall has destroyed all of the seized products [in *United States* v. *Undetermined Quantities of Drugs*, 455 U.S. 902 (1982)] with expired shelf lives or shelf lives of less than three months" (Resp. Br. 8 n.11). Counsel has been misinformed. No order has issued directing the Marshal to destroy the drugs involved in that case and the Marshal has informed FDA that no destruction has taken place. In any event, the case continues to present a live controversy for the reasons stated in our opposition to the suggestion of mootness. See *Havens Realty Corp.* v. *Coleman*, No. 80-988 (Feb. 24, 1982), slip op. 5-6.

Moreover, respondents' expert admitted at the preliminary injunction hearing in this case (Tr. 219; see Gov't Br. 24 n.30) that there has been virtually no testing of Generix's products; there is thus no logical or legal basis for presuming that they are safe and effective.[5] Indeed, the district court expressly found (Pet. App. 20a) that respondents' products containing six specified active ingredients "have not been tested" and are not generally recognized as safe and effective. The Act, which reflects Congress' conclusion that the public should not be exposed to drugs that *may* be

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[5]See Gov't Br. 23 n.29. Respondents would distort settled principles by arguing that the government must bear the burden of proving that these untested and potentially unsafe and ineffective drugs are in fact unsafe and ineffective (Resp. Br. 4, 6, 10). To the contrary, since the passage of the first "new drug" provision in 1938, the initial responsibility for establishing the requisite safety (and, since 1962, the effectiveness) of drugs has rested squarely on those who propose to market them. This is consistent with the common-sense rule that the party who controls the relevant facts bears the burden of proof. It would be especially unreasonable to place on FDA the burden of proving that an unapproved new drug is unsafe. In the absence of the required NDA, FDA would have no regularized mechanism for knowing that the drug will be sold; in addition, FDA would not know what the components of the unapproved drug product were, how it was manufactured, or what tests, if any, of its safety and effectiveness had been conducted. Under Generix's interpretation , manufacturers of untested drugs would be rewarded for selling them without approval if they could thereby shift to the government the burden of proving the lack of safety and effectiveness of drugs that should never have been sold. Such proof—which is in any event irrelevant—may not be available because harmful results, other than the most dramatic, may not be attributed by doctors to unknown generics (Tr. 89-90). In most cases where a drug does not achieve the desired result, the doctor will simply switch the patient to another product and will not report a problem unless he sees it frequently and recognizes that the generic is the cause. Tr. 89-91; *United States* v. *Premo Pharmaceutical Laboratories, Inc.*, 511 F. Supp. 958, 985 (D.N.J. 1981).

unsafe, prohibits the marketing of such drugs.[6] In the context of other legislation that has a similar "remedial orientation [and] is prophylactic in nature," this Court has recognized that "[t]he Act does not wait for [a patient] to die or become injured. It authorizes the promulgation of health and safety standards and the issuance of citations in the hope that these will act to prevent deaths or injuries from ever occurring." *Whirlpool Corp.* v. *Marshall*, 445 U.S. 1, 12 (1980). See *Atlas Roofing Co.* v. *Occupational Safety and Health Review Commission*, 430 U.S. 442, 444, 445 (1977).

II. THE LITERAL LANGUAGE OF THE ACT REQUIRES PREMARKET APPROVAL OF GENERIC DRUGS

A. Respondents' argument is premised on the notion that the Act's definition of "drug" includes only active ingredients and not drug products. As we have shown in our main brief (Gov't Br. 16-18), this argument is refuted by the plain language of 21 U.S.C. 321(g)(1)(B). Generic drug products—and not merely their active ingredients—are literally "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man

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[6]The burden of obtaining FDA approval of a generic product is not nearly so difficult as Generix suggests. As the court of appeals noted in *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, 629 F. 2d 795, 805 (2d Cir. 1980), "FDA has sought to minimize the cost and delay in obtaining approval for 'me-too' drug products by permitting the proposed marketer to file an ANDA [abbreviated new drug application] instead of an NDA [new drug application] * * *." See Gov't Br. 38-41. The 13 year average time from first synthesis to FDA approval of a new pioneer drug, referred to by Generix (Resp. Br. 4 n.5), bears little relationship to the approval time for generic products of the type at issue here. See note 17, *infra*.

* * *."[7] Narrowing this statutory language, as respondents propose, would be directly contrary to this Court's conclusion in *United States* v. *An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784 (1969), that "Congress fully intended that the Act's coverage be as broad as its literal language indicates—and equally clearly, broader than any strict medical definition might otherwise allow." 394 U.S. at 798. The Court, therefore, held that "the lower courts erred in refusing to apply the Act's language as written" (*ibid.*), and that a paper disk impregnated with an antibiotic was a "drug" within the meaning of 21 U.S.C. 321(g)(1)(B).[8]

B. Moreover, the term "drug" cannot be limited to active ingredients because such a narrow definition could not reasonably be applied to all of the contexts in which the term "drug" is used in the Act. As we have shown in our main brief (Gov't Br. 19-21), the statutory provisions

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[7]Respondents also contend that the term "articles" in subsections (A) and (B) of 21 U.S.C. 321(g)(1) is similarly limited to active ingredients (Resp. Br. 16-21). The flaws in this reasoning are obvious. First, the formularies referred to in Section 321(g)(1)(A) do not, as the court of appeals thought (Pet. App. 5a), recognize only active ingredients. Indeed, respondents concede (Resp. Br. 18 & n.20) that Section 321(g)(1)(A) encompasses "official preparations" and "dosage forms" as well as active ingredients. This is a significant concession because "official preparations" and "dosage forms" contain both active and inactive ingredients, thus eliminating a basic premise of respondents' theory. Second, even if Section 321(g)(1)(A) included only active ingredients, that would not limit the ordinary meaning of the word "article" as used elsewhere in Section 321(g)(1), such as subsections (C) and (D) ("articles intended for use as a component of any articles specified in clauses (A), (B), or (C) of this paragraph"). Cf. 21 U.S.C. 355(b)(2). Under respondents' construction, subsection (D) would be meaningless; because active ingredients are not composed of other active ingredients, subsection (D) necessarily includes inactive ingredients. See Gov't Br. 16-18.

[8]The definition embraced the inactive ingredients (including the paper disk) and was not limited to the active ingredient.

governing NDAs (21 U.S.C. 355(b) through (e)) can be applied only to drug products, not to active ingredients. In addition, the misbranding and adulteration provisions of the Act make it clear that a "drug" is an entity that may contain inactive ingredients. Thus, for example, a "drug" is misbranded if it contains two or more ingredients and does not list on its labeling each active ingredient and certain other specified ingredients "whether active or not." 21 U.S.C. 352(e)(1)(A)(ii). Similarly, a "drug" is adulterated within the statute's meaning if it bears or contains "for purposes of coloring only" an unsafe color additive. 21 U.S.C. 351(a)(4). A color additive included for coloring purposes only is, of course, an inactive ingredient, and, like other inactive ingredients, is part of a drug product, but not part of an active ingredient.

C. Generix's argument "would create a loophole in the statute that Congress simply did not intend to create." *United States* v. *Naftalin*, 441 U.S. 768, 777 (1979). See *United States* v. *Rutherford*, 442 U.S. 544 (1979) (refusing to find an implied exemption from the new drug approval requirements of 21 U.S.C. 321(p)(1) and 355). When the definition of the term "drug" is read, as it must be, in context of the whole Act, it is clear Congress did not intend to create the exception for which Generix argues. See *Rubin* v. *United States*, 449 U.S. 424, 431 (1981); *Philbrook* v. *Glodgett*, 421 U.S. 707, 713 (1975); *Richards* v. *United States*, 369 U.S. 1, 11 (1962).

III. THE LEGISLATIVE HISTORY OF THE ACT IS CONSISTENT WITH ITS LITERAL LANGUAGE

A. As this Court held in *United States* v. *An Article of Drug . . . Bacto-Unidisk, supra*, 394 U.S. at 792, in view of the Act's "broad remedial purpose," its language should not not be given "a narrow, restrictive reading in the absence of

congressional direction to do so." The legislative history of the Act's new drug provisions (see Gov't Br. 27-33), reveals no Congressional intention to except generic drug products from the Act's prohibition on marketing new drugs without prior FDA approval.[9]

B. Generix refers, as did the court of appeals, to a statement in the 1938 House Report (H.R. Rep. No. 2139, 75th Cong., 3d Sess. 9 (1938); Resp. Br. 22-23; Pet. App. 9a) that the Act's new drug provisions were not a "license provision" (see Resp. Br. 21-26). When viewed in the context in which it was made, this snippet from the legislative history provides no support for respondents' contention that individual drug products are exempt from premarket review.

In 1937, the Secretary of Agriculture recommended a statutory provision requiring affirmative approval by FDA before any new drug could be marketed. See S. Doc. No. 124, 75th Cong., 2d Sess. The Secretary (who then had responsibility for FDA) referred to this affirmative approval provision as "[l]icense control of new drugs" (*id.* at 9-10; Resp. Br. 22). Although bills containing this provision were introduced (see, *e.g.*, H.R. 9341, 75th Cong., 3d Sess. (1938)), this procedure was replaced in the Act ultimately passed: instead of requiring agency approval, the Act provided that if FDA took no action within 60 days (subject to extension to 180 days) after an NDA was filed, the application automatically became effective and the subject drug

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[9]See also *United States* v. *Rutherford, supra*, 442 U.S. at 552 (legislative history does not indicate Congressional intent to limit applicability of new drug provisions); *United States* v. *An Article of Drug . . . Bacto-Unidisk, supra*, 394 U.S. 793-798 (legislative history shows that Congress did not intend to limit the literal language of the term "drug"). Cf. *Rose* v. *Lundy*, No. 80-846 (May 3, 1982), slip op. 8; *FBI* v. *Abramson*, No. 80-1735 (Mar. 24, 1982), slip op. 10 n.7; *Philbrook* v. *Glodgett, supra*, 421 U.S. 707, 713 (1975); *FTC* v. *Fred Meyer, Inc.*, 390 U.S. 341, 349 (1968).

could be marketed. Federal Food, Drug, and Cosmetic Act, ch. 675, Section 505, 52 Stat. 1052. It was this lack of an affirmative approval requirement that differentiated the so-called "license" provision originally sought by the Secretary from the statute enacted in 1938.[10]

The situation was altered significantly, however, in 1962. In that year, Congress amended the Act to require affirmative FDA approval of an NDA before a product could be marketed. See 21 U.S.C. 355(a) and (c); Gov't Br. 31. Thus, the so-called "licensing" proposal that was rejected in 1938 became law in 1962 and the comments respondents quote from the 1938 House Report have no bearing on the law, as amended, that governs this case.[11]

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[10]Contrasting the Secretary of Agriculture's proposed "license" provisions with those that were adopted, Representative Coffee commented (83 Cong. Rec. 7784 (1938)):

> How about the other recommendations of the Secretary to protect the public? The first and most important was license control of new drugs to insure that they will not be distributed until experimental and clinical tests have shown them to be safe for use. My own bill provided for such license control. Following the Secretary's report, my colleague from Kentucky [Mr. Chapman], who has been waging a courageous fight for adequate legislation in this field, introduced a good bill along the line of the Secretary's recommendations.
>
> Yet what do we find in the House bill? A backhanded type of control that puts the real responsibility on the Government. The manufacturer who proposes to put out a new drug product may simply turn over to the Department of Agriculture a sample of his product, together with the labeling he intends to use and what he considers proof of its harmless character when used as he directs. If at the end of 60 days the Secretary of Agriculture has not denied his application, he can go ahead with it.

[11]Respondents also argue that the Act passed by Congress in 1938, although it was an attempt to prevent any recurrence of the Elixir Sulfanilamide tragedy, required a showing of the safety of *only* the active ingredient of a drug. As we have explained (Gov't Br. 27-29), such

C. Generix is likewise mistaken (Resp. Br. 32-33) in dismissing as irrelevant Senator Kefauver's statements expressing his understanding that FDA ordinarily approved, as safe, different "brands [that] are identical generically," and asking that such product-specific approval be required for effectiveness as well (106 Cong. Rec. 12665 (1960); see Gov't Br. 30-31). The suggestion is that the Senator was commenting on a bill containing "product licensing provisions" that were not enacted. The bill he was discussing (S. 3677, 86th Cong., 2d Sess. 1-2 (1960)), had two basic purposes: first, to amend the "new drug" definition to add the concept of effectiveness to the "general recognition" requirement, and, second, to provide an *establishment* licensing system to deal with manufacturing practice problems (see Gov't Br. 37 n.46). While the establishment licensing provisions were not enacted, the language immediately following that quoted in our main brief (*id.* at 30-31) makes it clear that Senator Kefauver was referring to the proposed "new drug" effectiveness amendment which, in revised form, did become law (see S. 1552, 87th Cong., 1st Sess. 12-13 (1961)). Senator Kefauver said (106 Cong. Rec. 12665 (1960) (emphasis added)):

> We cannot afford anything but the best drugs. There is not and should not be any room in America for first-, second-, and third-class drug products. *In passing on efficacy as well as safety in new drug applications* the Food and Drug Administration could go a long way toward eliminating any basis for the contention that there are second- and third-class drugs.

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a statute would not have prevented the marketing of Elixir Sulfanilamide itself. Generix's statement that the toxic component in Elixir Sulfanilamide was an active ingredient (Resp. Br. 21 n.24) is incorrect. An active ingredient is one that "is intended to" furnish the pharmocological activities or other direct effect. 21 C.F.R. 210.3(b)(7). Diethylene glycol, used as a solvent in Elixir Sulfanilamide, was not intended to produce a direct effect nor was it labeled as an active ingredient in Elixir Sulfanilamide. S. Doc. No. 124, 75th Cong., 2d Sess. 2 (1937).

D. Finally, contrary to Generix's assertion (Resp. Br. 23, 29-33), the legislative history does not indicate that the Act's adulteration provisions were considered by Congress to address the dangers inherent in the marketing of untested drug products.[12] Rather, the new drug and the adulteration provisions were adopted in 1938 and strengthened in 1962 to deal with different aspects of the Congressional desire to assure that all drugs on the market are safe and effective (see Gov't Br. 35-38). The new drug provisions are designed to require that drugs be proven safe and effective before they reach the public. The adulteration provisions, however, are aimed at post-introduction problems; they focus on assuring that drugs already on the market are what they purport to be. These provisions have no application to premarketing review and were not intended to substitute postmarketing enforcement tools for adequate premarketing scrutiny.

IV. FDA CONSISTENTLY HAS APPLIED THE "NEW DRUG" DEFINITION TO PRODUCTS AND NOT TO ACTIVE INGREDIENTS ALONE

A. Generix's assertion that "FDA has consistently interpreted 'new drug' as relating to active ingredients, not to specific products" (Resp. Br. 36; emphasis omitted) is simply incorrect. To the contrary, shortly after passage of the 1938 Act, the Department of Agriculture published a

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[12]Indeed, if one accepts respondents' contention that the term "drug" refers only to active ingredients, then even the adulteration provisions, which use the term "drug," would have no application to drug products. This is clearly not what Congress intended when it enacted a law to keep potentially harmful drug products from being marketed initially (new drug provisions) or from further sale if they were made improperly (adulteration provisions).

regulation (3 Fed. Reg. 3161-3162 (1938))[13] stating that any change in, *inter alia*, the inactive ingredients from which a drug is formulated may make that drug a "new drug."[14] This regulation has remained substantially unchanged to the present day and now appears at 21 C.F.R. 310.3(h).

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[13]That regulation was promulgated at the time of the statute's first implementation "by the men charged with the responsibility of setting its machinery in motion, of making the parts work efficiently and smoothly while they are yet untried and new," *Andrus* v. *Shell Oil Co.*, 446 U.S. 657, 667-668 (1980), quoting *Norwegian Nitrogen Products Co.* v. *United States*, 288 U.S. 294, 315 (1933), and is thus entitled to considerable weight. As this Court recently observed, "[w]e have often noted that the interpretation of an agency charged with the administration of a statute is entitled to substantial deference." *Blum* v. *Bacon*, No. 81-770 (June 14, 1982) slip op. 10. See also, *e.g.*, *E.I. duPont de Nemours & Co.* v. *Collins*, 432 U.S. 46, 54-55 (1977); *Red Lion Broadcasting Co.* v. *FCC*, 395 U.S. 367, 381 (1969); *Udall* v. *Tallman*, 380 U.S. 1, 16 (1965); *Investment Company Institute* v. *Camp*, 401 U.S. 617, 626-627 (1971). This principle is particularly compelling where, as here, there is a "longstanding and consistent administrative interpretation." *Zenith Radio Corp.* v. *United States*, 437 U.S. 443, 450 (1978).

[14]Another contemporaneous interpretation of this statute was provided by the chief of the FDA Drug Division from 1937 to 1940, who administered the regulation of drugs during the years after the passage of the statute:

> Whatever influences the safety of a drug has a bearing on the application of 505 [the approval provision, 21 U.S.C. 355]. This section, in our judgment, applies to drugs as individual articles, not as collective groups. We have been repeatedly asked by drug manufacturers and others whether it is necessary to file an application for, let us say, sulfapyridine, when other manufacturers have already placed sulfapyridine on the market. It is our interpretation of the Congressional intent that each manufacturer of sulfapyridine or any other drug must file his own application.

Klumpp, *The Influence of the Food, Drug and Cosmetic Act on the Marketing of Drugs*, 6 Conn. St. Med. J. 3, 3-4 (1942).

B. Despite that consistent official interpretation of the "new drug" provision, Generix argues that because FDA in two situations has treated drugs as classes, rather than on a strict product-by-product basis, it should be deemed to have adopted Generix's view that the term "new drug" applies to active ingredients rather than to drug products. Neither the early FDA practice of issuing "not new drug" letters concerning prescription generic drugs nor the agency's present monograph approach to over-the-counter (OTC) products, however, represents a departure from the application of the term "new drug" to drug products. Rather, in both situations, FDA, as a matter of enforcement policy, implemented procedures to expedite the process of making judgments about the "new drug" status of individual products in a way that, in the agency's view, best utilized its limited resources to protect the public health.

1. Within a few years after passage of the Act, difficulties in processing NDAs, exacerbated by war-related staff shortages, led FDA to issue, and manufacturers increasingly to request, advisory opinions, referred to as "not new drug" letters. These letters expressed the agency's view that particular drug products—usually generic versions of approved drugs—were not themselves new drugs and could be marketed without FDA approval. See generally 40 Fed. Reg. 26142-26143 (1975). This practice, however, did not in any way reflect an FDA view that only active ingredients—rather than drug products—could be new drugs. The "not new drug" letters covered particular drug products; they were not issued for active ingredients. Indeed, in some cases FDA concluded that generic copies of approved drugs were *not* generally recognized among experts as safe and thus *were* "new drugs" that required NDAs. See 40 Fed. Reg. 26142-26143 (1975).

Where "not new drug" letters were issued for generic products, they apparently reflected FDA's conclusion, on the basis of scientific knowledge at that time, that experts generally would recognize the safety and effectiveness of some generic copies based on evidence obtained, in large part, from the testing and marketing of pioneer products.[15] That view of the evidence on which expert general recognition could be based, however, was not a departure from the principle that each product must be judged individually to determine whether it is a new drug, and it does not demonstrate a conclusion that the "new drug" provisions apply only to active ingredients.[16] Nor does FDA's past practice of issuing "not new drug" letters compel the FDA to ignore

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[15]As this Court stated in *Hynson*, one prerequisite for "general recognition" of a drug is the existence of adequate and well-controlled investigations showing that drug to be effective (412 U.S. at 632-634). Generix states that "[t]he purpose of adequate and well-controlled investigations is to demonstrate the effectiveness of a product's active ingredient, not of any particular formulation of that active ingredient" (Resp. Br. 43). Generix provides no support for that conclusion, which is in fact demonstrably incorrect, as we explained in our opening brief (Gov't Br. 5-8, 19-22, 26). As the government's expert testified, what an expert recognizes as safe and effective is a drug product, not its active ingredient (Tr. 102-103). In fact, it is now required in many scientific journals that a published study include not only the manufacturer of the product studied but the lot number and the dosage form (Tr. 105-106).

[16]During the years when FDA issued "not new drug" letters, it continued to judge products rather than active ingredients. Thus, in 1956, an FDA official responsible for administering the new drug provisions stated that: "Not only the active ingredients of a product but also the so-called inactive ingredients, such as a menstruum, excipient, carrier, or coating, may cause it to be a new drug." Smith, *What Is a New Drug under the Food, Drug, and Cosmetic Act?* 89, 90 in *The Impact of the Food and Drug Administration on Our Society* (H. Welch & F. Marti-Ibanez eds. 1956). He emphasized that "not new drug" determinations were consistent with the "newness" regulation promulgated in 1938 because that regulation stated that the "new drug" status of a drug may arise by virtue of changes in the various listed factors. Smith, *supra*, at 91.

the best current medical knowledge in determining whether there is expert general recognition of a particular product. As the record in this case shows, expert general recognition of the safety and effectiveness of a generic prescription drug could not today be based solely on evidence concerning the pioneer. It is not disputed that bioavailability differences between two products containing the same active ingredient can make any extrapolation from one to the other entirely inappropriate[17] for prescription products, which are by definition potentially dangerous.[18]

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[17]Extrapolation from data concerning a pioneer drug to the generic copy is appropriate only if adequate data have been developed to show that the copy is bioequivalent to the pioneer drug. Thus it is theoretically possible for a generic drug to achieve "general recognition" among experts if 1) there are sufficient safety and effectiveness data about the pioneer, 2) there are bioavailability data which show the copy to be equivalent to the pioneer, 3) the data about the pioneer and the bioequivalence data are published in the scientific literature and thus available to experts generally, and 4) there is a clear consensus in the expert community that the data show the generic copy to be safe and effective. As a practical matter, bioavailability data are seldom published in the scientific literature and "general recognition" based on published bioavailability data therefore is unlikely. The alternative, followed by generic manufacturers that seek abbreviated new drug applications (ANDAs), is to submit the bioavailability data to FDA where the data can be analyzed by FDA experts. In approving such ANDAs, the experts at the agency properly rely on the showing of bioequivalence to conclude that it is appropriate to extrapolate from the basic data (*i.e.*, safety studies and adequate and well-controlled effectiveness investigations) concerning the pioneer product to find that the generic copy has been shown to be safe and effective. Thus, Generix is wrong in suggesting that accepting the government's position here would require the inclusion of full adequate and well-controlled investigations in each ANDA (Resp. Br. 43).

[18]The Act prohibits the dispensing, except on prescriptions, of certain habit-forming drugs and of any drug which "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug" or "is limited by an approved [NDA] to use under the professional supervision of a practitioner licensed by law to administer such drug." 21 U.S.C. 353(b)(1)(B) and (C).

2. FDA's monograph approach to approval of over-the-counter drugs[19] is not inconsistent with its position that the term "new drug" applies to generic drug products. The monograph system is the result of an FDA determination that the statutory standard of expert general recognition—which applies to all drugs—may be satisfied by OTC drugs through a more simplified procedure than that applied to the more powerful prescription drugs. OTC drugs, by definition, are not sufficiently dangerous to require medical supervision (see note 18, *supra*) and they generally are used to treat self-limiting conditions. Accordingly, in FDA's view, experts would recognize OTC products containing specified active ingredients in specified amounts and "suitable" inactive ingredients (see 21 C.F.R. 330.1(e)) as safe and effective on the basis of testing and experience with other products containing the same ingredients.

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[19]OTC drugs are not involved in this case (see Gov't Br. 41 n.50). There is no evidence in the record concerning OTC drugs, and all of the drugs discussed in the district court and court of appeals opinions are prescription drugs. Nevertheless, Generix suggests that the complaint in this action sought an injunction against the distribution of OTC drugs as well as unapproved prescription drugs (Resp. Br. 3 n.4). That is not accurate. The relief sought was a prohibition against the introduction or delivery for introduction into interstate commerce of drugs as to which respondents had received notice by letter, Federal Register announcement, or any other action by the FDA that the drug was a "new drug," unless that drug was approved or satisfied the investigational drug exemption in the statute (J.A. 17-18). The requested relief would have permitted Generix to market drugs that other distributors are allowed to market, including OTC products that conform to OTC monographs or that are the subject of contemplated monographs that have not yet been finalized. A decision for the government in this case would not require manufacturers to obtain approval of NDAs before marketing generic aspirin (see Resp. Br. 3 n.4). Under the agency's enforcement policy, such applications are not required for any OTC aspirin product until the OTC analgesic monograph is completed. When it is completed, applications would not be required for aspirin products that conform to the monograph.

For these reasons, FDA, with the aid of expert panels, is developing monographs that characterize with particularity OTC *products* that can be classified as "generally recognized" by experts as safe and effective.[20] These monographs represent the most appropriate and efficient means of applying the Act to OTC drugs by, in effect, formulating in advance working definitions of general expert recognition for specified products. In implementing the OTC monograph system, FDA has concluded that experts generally would consider additional evidence of bioequivalence among conforming OTC drugs, beyond that supplied by adherence to monograph standards, as unnecessary. The OTC procedures thus fully apply the statutory standards in a manner consistent with the Act's intent.

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[20]See *e.g.*, 21 C.F.R. 331.1: "An over-the-counter antacid *product*" that conforms to the monograph is generally recognized as safe and effective (emphasis added). In the mid-1970s, FDA considered, but never implemented, a plan to create "not new drug" monographs for some prescription drugs similar to the monographs FDA is developing for OTC products. In support of that proposed policy change, some FDA officials suggested that generic prescription drugs that qualified for submission of ANDAs (see Gov't Br. 38-41) had, in effect, a status similar to the drugs that, in previous decades, had received "not new drug" letters. Generix quotes a former FDA official as stating that the Federal Register notices that allow ANDAs to be submitted for generic copies of drugs approved prior to 1962 " 'impl[y] that the generic drug is generally recognized as safe and effective, and hence is not a new drug because no additional safety and effectiveness data need be submitted in the ANDA,' " (Resp. Br. 39, quoting McEniry, *Drug Monographs*, 29 Food Drug Cosm. L.J. 166 (1974)). The quoted statement, however, does not accurately describe the notices. Rather, all of them contain statements to the effect that the generic drugs for which ANDAs may be submitted "are regarded as new drugs (21 U.S.C. 321(p)). * * *. A new—drug application is required from any person marketing such drugs without approval." See, e.g., 37 Fed. Reg. 13562 (1972).

CONCLUSION

The decision of the court of appeals should be reversed.

Respectfully submitted.

REX E. LEE
Solicitor General

OCTOBER 1982

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Amicus Brief

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No. 81-1222

IN THE

Supreme Court of the United States

October Term, 1981

UNITED STATES OF AMERICA,

Petitioner,

v.

GENERIX DRUG CORPORATION, *et al.*,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Eleventh Circuit

MOTION FOR LEAVE TO FILE BRIEF AMICUS CURIAE ON BEHALF OF THE GENERIC PHARMACEUTICAL INDUSTRY ASSOCIATION IN SUPPORT OF PETITIONER AND BRIEF OF THE GENERIC PHARMACEUTICAL INDUSTRY ASSOCIATION AS AMICUS CURIAE IN SUPPORT OF PETITIONER

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On Writ of Certiorari to the United States Court of Appeals for the Eleventh Circuit

MOTION FOR LEAVE TO FILE BRIEF AMICUS CURIAE ON BEHALF OF THE GENERIC PHARMACEUTICAL INDUSTRY ASSOCIATION IN SUPPORT OF PETITIONER

The Generic Pharmaceutical Industry Association, Inc. ("GPIA") respectfully moves this Court, pursuant to Rules 36.3 and 42 of the Rules of this Court, for leave to file the annexed brief amicus curiae. In support of this motion, GPIA states:

1. The Generic Pharmaceutical Industry Association is a group of independent generic drug manufacturers, dis-

tributors and retailers, who organized in 1980 to coordinate their efforts to eliminate legal impediments delaying and blocking the distribution and sale of generic drugs. GPIA members account for a substantial portion of the sales of independently manufactured generic prescription drugs.

2. Generic substitution laws, which encourage substitution of lower-cost, therapeutically equivalent generic drugs for unpatented, higher-priced, and heavily promoted brand-name drugs, are vital to the public as a means of reducing health care costs and likewise vital to the economic welfare of GPIA members.

3. For generic substitution laws to be effective, physicians must have confidence in the generics. The continued viability of state generic substitution laws and the credibility of generics depends upon maintaining existing requirements that assure the safety and efficacy of such drugs.

4. The issue raised in this case—whether the FDA will continue to assure the safety and efficacy of all drugs or only of those drugs with new active ingredients—transcends the specific parties and facts and will have a major economic impact on the generic pharmaceutical industry and on consumers of prescription drugs.

5. Prior to the Court of Appeals' decision in this case, it was generally believed that generic drugs required the same supervision by the United States Food and Drug Administration as other drugs. This permitted consumers and State Legislatures to have confidence in the safety and efficacy of generic pharmaceuticals and ensured a wide market for generics.

6. The decision below would undermine this confidence and, therefore, would establish a substantial barrier to marketing generic drug products. As actual and potential manufacturers and distributors of generics, the economic position of GPIA members will be greatly affected by this Court's decision.

7. The United States has consented to the filing of GPIA's brief as amicus curiae and its consent is on file with the Clerk.

For these reasons, GPIA respectfully requests that its motion for leave to file the annexed brief amicus curiae be granted.

Dated this 12th day of April, 1982.

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On Writ of Certiorari to the United States Court of Appeals for the Eleventh Circuit

BRIEF OF THE GENERIC PHARMACEUTICAL INDUSTRY ASSOCIATION AS AMICUS CURIAE IN SUPPORT OF PETITIONER

Interest of Amicus Curiae

The Generic Pharmaceutical Industry Association, Inc. ("GPIA"), is a trade association of generic drug manufacturers and distributors formed in 1980.[1] Its purpose

1. Its members, in compliance with Rule 28.1 of the Rules of this Court, are: Biocraft Laboratories, Inc.; Bolar Pharmaceutical Co., Inc.; Cord Laboratories, Inc.; Darby Drug Co., Inc.; Mylan Pharmaceuticals Inc.; Revco D.S., Inc., Henry Schein Inc.; Zenith Laboratories, Inc.

is to help ensure that safe and effective generic drugs reach the public and that legal obstacles preventing the distribution and sale of generics are resolved. GPIA members manufacture and distribute a substantial portion of the generic drugs on the national market. They have a substantial interest in this case, because its outcome will directly impact on how the public views the safety and efficacy of generic drugs and thus whether the public continues to purchase them.

The value of generic drugs in reducing the cost of health care and thereby protecting the public has been widely recognized: Indeed, 48 states, the District of Columbia and Puerto Rico have laws designed to encourage the substitution of safe and effective generics for higher-priced but therapeutically equivalent brand-name drugs (see Appendix).

Historically, the public and the states have only had confidence in generic drugs when generics were supervised by the United States Food & Drug Administration ("FDA") and satisfied the same safety and efficacy standards as required of other drugs. Effective use of laws permitting the substitution of lower-priced generic drugs for the more expensive, heavily promoted brands is based in large measure on the confidence of the physician prescribing the generic. For generics to retain their credibility, therefore, FDA premarketing approval, which currently assures their safety and efficacy, is vital.

The decision below fails to recognize this and, by undercutting the protection to the public, also gravely imperils the public's continued confidence in generics and the market

for generics. As manufacturers and distributors of generic drugs, the GPIA members have a tremendous economic stake in the decision of this Court.

Summary of Argument

Legislation encouraging the substitution of less expensive generic drugs, as well as the public's acceptance of generics, has been made possible because the safety and efficacy of generics has been assured by the federal requirement of premarketing evaluation and approval.

The premarketing approval requirement serves the Congressional objective of promoting the availability of safe, effective, inexpensive generics, and is mandated by the statute.

Premarketing approval need not cause counterproductive delays. The FDA's procedure of utilizing established scientific literature in its premarketing evaluations, which has been upheld by the courts, expedites such approval.

ARGUMENT

I. Premarketing Approval of Generic Pharmaceuticals Is Necessary to Ensure That Safe, Effective and Inexpensive Generics Are Available to the Public.

Prior to 1962, most states had antisubstitution laws designed to discourage the use of generic pharmaceuticals, even though generic drugs were much less expensive than their brand-name counterparts.[2] These antisubsitution laws reflected public fear that generics would not perform

2. See Federal Trade Commission, *Staff Report, Drug Product Selection*, 145 *et seq.* (1979) (hereafter "FTC Staff Report").

properly due to faulty active or inactive ("excipient") ingredients;[3] "active" ingredients are the therapeutic agents, while the "inactive" or "excipient" ingredients protect, dilute or convey them. As a result of these statutes, the public routinely paid the higher prices charged for heavily advertised, brand-name prescription drugs.[4]

Partially in response to this situation, the 1962 amendments to the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 321, *et seq.*) ("the statute") required increased supervision of pharmaceutical manufacturing and marketing by the FDA, thereby assuring good manufacturing practices as well as the safety and efficacy of all prescription drugs. The assurances provided by FDA action under these amendments led to greatly increased public acceptance of generics. By 1978, the FDA reported:

> "All drugs, whether they are sold under their brand names or their generic names, must meet the same FDA standards for safety, strength, purity and effectiveness. And all drug manufacturers, big or small, are subject to FDA inspection and must follow the Agency's Current Good Manufacturing Practice Regulations. That is why FDA believes there is no significant difference in quality between generic and brand name drugs.
>
> * * *
>
> Not only must each drug meet FDA requirements, so must each drug plant. All firms—large and small—must register with FDA; all are subject to periodic

3. See H. Rep. No. 2139, 75th Cong., 3d Sess. (1938), discussed in Petition for Certiorari on behalf of the United States at 16 and other authorities cited at n. 25.

4. See generally *FTC Staff Report*, n. 2 *supra*, at 196-219; *Virginia State Board of Pharmacy* v. *Virginia Citizens' Consumer Council, Inc.*, 425 U.S. 748, 754 (1976).

inspection, and all must follow FDA Good Manufacturing Practice Regulations (GMP's) that touch on every aspect of making drugs, from building maintenance to quality control. These regulations apply to all producers and are intended to assure that all drugs meet the same standards of safety, strength, purity, and effectiveness. *These requirements, in fact, were built into the 1962 amendments to the food and drug laws for the very purpose of encouraging physicians to make wider use of generic drugs in order to lower the cost of medical care*, according to the cosponsor of the legislation, the late Senator Estes Kefauver.'"[5] (emphasis added).

As a result of this climate of increased public confidence, 48 states, the District of Columbia and Puerto Rico have adopted laws permitting or requiring pharmacists to substitute less expensive generics for brand-name drugs when permitted by the prescribing professional.[6] The result has been to help limit the cost of health care.[7]

The decision of the Court of Appeals below seriously threatens the continued safety and efficacy of generic phar-

5. Hecht, FDA Office of Consumer Affairs, *Generic Drugs: How Good Are They?*, FDA Consumer Magazine, Feb., 1978, pp. 17-18; see also U.S. Dept. of Health, Education and Welfare (2/7/69), *Final Report, Task Force on Prescription Drugs.*

6. Forty-eight states, the District of Columbia and Puerto Rico have similar laws. See, Appendix; *Competition in the Drug Industry: Hearings Before the Subcom. on Oversight & Investigations of the House Comm. on Energy & Commerce*, 97th Cong., 1st Sess. 13 (3/10/81); Warner, *Consumer Protection and Prescription Drugs: The Generic Drug Substitution Laws*, 67 Ky.L.J. 384 (1978-9). Such laws were upheld in, *e.g.*, *PMA* v. *Whalen*, 54 N.Y.2d 486 (1981); *Pharmaceutical Society of the State of New York* v. *Lefkowitz*, 586 F.2d 953 (2d Cir. 1978).

7. *E.g.*, in New York alone, an estimated $60 million annually under N.Y. Educ. L. §§ 6810-6816-a, DeNuzzo, *Substitution—The New York Experience*, 16 Medical Marketing & Media 25-29 (1981).

maceuticals and the anti-inflationary savings they provide.[8] The decision below, contrary to the weight of authority[9] and to the wording of the statute itself, holds that premarketing approval of drugs is only required when the active ingredient is new.[10]

Although the Court of Appeals correctly recognized that one of the objectives of the 1962 amendments was to promote generic competition and to reduce the cost of pharmaceuticals to the public,[11] its decision undermines these very objectives. By striking at the heart of the statutory protection provided by the statute and the 1962 Amendments, the court below has undercut the basis of public confidence in generics and the basis of the state substitution laws.

To take merely one example, in *PMA* v. *Whelan*, 54 N.Y.2d 486 (1981) the New York State Court of Appeals

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8. ". . . the local benefit is the potential saving to New York patient-consumers based on the price differentials between brand name drugs and lower-priced generic equivalents, which represents a legitimate interest. See *Virginia State Board of Pharmacy* v. *Virginia Citizens Consumer Council*, 425 U.S. 748, 763-64, 96 S.Ct. 1817, 48 L.Ed.2d 346 (1976)."

Pharmaceutical Society of the State of New York v. *Lefkowitz*, 586 F.2d 953, 957 (2d Cir. 1978).

9. The relevant authorities are discussed at length in the District Court opinion, 498 F.Supp. 288 (S.D. Fla. 1980) and such discussion need not be repeated here.

10. The definitions of "drug" and "new drugs" in 21 U.S.C. § 321(g) and 21 U.S.C. § 321(p) contain no distinctions as to active or inactive ingredients, incipients or excipients.

11. S. Rep. No. 1744, 87th Cong., 2d Sess. (1962), U.S. Code Cong. & Ad. News 2893-94, quoted by the Court of Appeals, 654 F.2d at 1118-1119; Note, *Drug Amendments of 1962—Generic Name Prescribing: Drug Price Panacea*, 16 Stan.L.Rev. 649, 651-52 (1963); 1962 U.S. Code Cong. & Ad. News 2898 (views of Senator Kefauver and others).

strongly relied on federal supervision in upholding the New York Generic Substitution Law, N.Y.L. 1977, ch. 776, amending N.Y. Educ. L. §§ 6810, 6816-a:

> "The FDA is given the responsibility of assuring the supply of safe and effective drugs on a national level (see US Code, tit 21, § 355.) This Federal agency has both superior expertise and extensive resources at its disposal, and the test it employs in certifying drugs as safe and effective is truly 'a rigorous one'. (*Weinberger* v. *Hynson, Wescott & Dunning*, 412 US 609, 630. [1973])" *Id.* at 495.

II. The Requirement of Premarketing Approval Is Consistent With Statutory Goals.

Both in general[12] and in the pharmaceutical field in particular,[13] our Congressionally articulated economic and public policy utilizes the open marketplace to maximize public welfare. This, of course, requires an "infrastructure" of necessary regulation to protect the public in those situations where the public is unable to protect itself. In light of the risk posed by unsafe or inefficacious pharmaceutical products, Congress has required the FDA to evaluate drugs for their safety and efficacy before they reach the consuming public.

The Court of Appeals correctly, if implicitly, recognized that the statute contemplates that competition be protected from unnecessary or unintended bureaucratic delays. But it erred in assuming that such delays are necessarily attendant to the premarketing approval of drugs

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12. *Catalano, Inc.* v. *Target Sales, Inc.*, 446 U.S. 643 (1980); *Nat'l Soc'y of Prof'l Eng'rs* v. *United States*, 435 U.S. 679 (1978).

13. See Note 11, *supra*.

which the statute mandates. The court below incorrectly assumed that pointless, duplicative and time consuming retesting and reevaluation would be involved each time an approved, safe and effective active ingredient was combined with a different inactive or excipient ingredient.

The statutory requirement of 21 U.S.C. § 355(b) that the safety and efficacy of "new" drugs be established by "full" reports of investigations has the requisite "generality and adaptability"[14] so that "rigorous"[15] assurance of the safety and efficacy of new drugs can be assured without wasteful duplication of previously known scientific work. To this end, the FDA permits applications for premarketing approval of new drugs ("New Drug Applications") to rely on data previously published in the scientific literature.[16] This policy has withstood numerous judicial challenges[17] and is properly being used by the FDA as a permanent technique for expediting the marketing of pharmaceuticals that are safe and effective.[18] Since scien-

14. Compare *Appalachian Coals* v. *United States*, 288 U.S. 344, 359-60 (1933) (Hughes, C.J.).

15. *Weinberger* v. *Hynson, Wescott & Dunning, Inc.*, 412 U.S. 609, 630 (1973).

16. 46 Fed. Reg. 27,396-397 (5/19/81); 45 Fed. Reg. 82,052 (12/12/80).

17. *Burroughs Wellcome Co.* v. *Schweiker*, 649 F.2d 221 (4th Cir. 1981); *American Critical Care* v. *Harris*, No. 81C-252 (N.D. Ill. 5/13/81); *Hoffman-LaRoche* v. *Harris*, 484 F.Supp. 58 (D.D.C. 1979); *American Hospital Supply Co.* v. *Harris*, Civil Action No. 79-2318 (D.D.C. 9/4/79); see also *Biocraft Laboratories, Inc.* v. *Harris*, CCH Food, Drug & Cosmetic Rptr. ¶ 38,089 (D.N.J. Jan. 12, 1981).

18. The FDA relies solely on recognized scientific data to satisfy the criteria of the Act for certain classes of nonprescription pharmaceuticals. 21 C.F.R. § 330.10. Similarly, the FDA allows abbrevi-

(footnote continued on next page)

tific literature is often available to establish expeditiously the safety and validity of generic versions of brand-name drugs, premarketing approval of such drugs assures the safety and efficacy of generics, without unduly delaying their marketing.

Ironically, the major barrier to the marketing of generics has not been the statute's premarketing approval requirement but, rather, the numerous litigations brought by brand-name competitors of generic drugs.[19] These competitors have used the courts in repeated, unsuccessful efforts to prevent the FDA from relying on established scientific data to facilitate the approval of safe and effective generics.[20]

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ated applications for pre-1962 drugs having known characteristics where data known to the FDA combined with published literature is sufficient. 21 C.F.R. § 314.1(a). Neither of these practices has been challenged to date. Moreover, public comment is to be sought on extending the latter procedure to post-1962 drugs. 45 Fed. Reg. 1765 (1/13/82).

19. Note 17, *supra*.

20. Since the federal food and drug laws are neither licensing laws, H. Rep. No. 2139, 75th Cong., 3d Sess. 9 (1938), quoted, 654 F.2d at 1118, nor designed to protect competitors, compare *Ass'n of Data Processing Service Organizations* v. *Camp*, 397 U.S. 150 (1970), these promoted brand manufacturers arguably do not properly have standing to challenge FDA policies for approving safe and effective generic substitutes for their products. *Id.* at 152-53. Nor does the statute provide or imply that they have a private right of action, *Cort* v. *Ash*, 422 U.S. 66, 78 (1975); *Sierra Club* v. *Morton*, 405 U.S. 727 (1972); see also *Transamerica Mortgage Advisors, Inc.* v. *Lewis*, 444 U.S. 11 (1979); *Touche Ross & Co.* v. *Redington*, 422 U.S. 560 (1979); *Cannon* v. *University of Chicago*, 441 U.S. 667 (1979). Compare also *Brunswick Corp.* v. *Pueblo Bowl-O-Mat, Inc.*, 429 U.S. 477 (1977).

Conclusion

Pre-marketing approval of all new drugs, including pharmaceuticals with differing excipients, is required by the plain meaning of the statute.

It is also required by the statutory objectives of assuring the public of the safety and efficacy of pharmaceuticals on the market and of promoting the availability of reliable and economical generic drugs.

The decision of the Court of Appeals to the contrary should be reversed.

Respectfully submitted,

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APPENDIX

APPENDIX

State Generic Substitution Acts

1. Alabama Code § 34-23-8 (1979)
2. Alaska Stat. § 08.80.295 (1976)
3. Arizona Rev. Stat. Ann. § 32-1963.01 (1979)
4. Arkansas Stat. Ann. § 72-1049 (1976)
5. California Business and Professions Code §§ 4047.6 and 4047.7 (1976)
6. Colorado Rev. Stat. § 12-22-124 (1978)
7. Connecticut Gen. Stat. Ann. §§ 20-185a through 20-185f (1976)
8. Delaware Code Ann. Tit. 24, § 2589 (1979)
9. Florida Stat. Ann. § 465.025 (1976)
10. Georgia Code Ann. §§ 79A-408.1 through 79A-408.5 (1978)
11. Hawaii Drug Product Selection Act, Hawaii Rev. Stat. Tit. 19, §§ 328-91 through 328-99 (1979)
12. Idaho Ann. §§ 18-479-446; 17-479-460 in acc. with § 37-2702(d) (1979) (see latest supplement)
13. Illinois Rev. Stat. ch. 111, § 4033 (1977)
14. Indiana—none
15. Iowa Stat. Ann. § 155.37 (1976)
16. Kansas Stat. Ann. § 65-1637a (1979)
17. Kentucky Rev. Stat. § 217.822 (1978)
18. Louisiana Rev. Stat. Ann. § 37-1225 (1979)
19. Maine Rev. Stat. Ann. Tit. 32, § 2806 (1979)
20. Maryland (Health) Code Ann. § 43-273A (1978)

21. Massachusetts Ann. Laws ch. 112, § 12D (Hichie/Law Co-op) (1976)

22. Michigan M.C.L.A. § 333.17755 (1978)

23. Minnesota Stat. Ann. § 151.21 (1975)

24. Mississippi Code Ann. §§ 75-29-701 through 75-29-709 (1979)

25. Missouri Drug Product Selection Law, Mo. Ann. Stat. § 338.056 (1979)

26. Montana Drug Product Selection Act, Mont. Rev. Codes Ann. Tit. 37, ch. 7, §§ 501-510 (1977)

27. Nebraska Drug Product Selection, Neb. Rev. Stat. §§ 71-54.01 through 71-54.08 (1977) (found in 1980 Supp.)

28. Nevada Rev. Stat. §§ 639.2581 through 639.2599 (1979)

29. New Hampshire Rev. Stat. Ann. ch. 146 § 6-b (1973)

30. New Jersey Stat. Ann. §§ 24:6E-6 and 24:6E-7 (1977)

31. New Mexico Stat. Ann. § 26-3-3 (1976)

32. New York—Chapter 776, Laws of 1976, N.Y. Educ. L. §§ 6810, 6816-a

33. North Carolina Gen. Stat. § 90-76.1-76.6 (see 1980 Supp.) (Article 4—Pharmacy)

34. North Dakota Cent. Code § 19-02.1-14.1 (1979)

35. Ohio Rev. Code Ann. § 4729.38 (1978)

36. Oklahoma—none

37. Oregon Rev. Stat. § 689.515 (1977)

38. Pennsylvania Stat. Ann. Tit. 35, §§ 960.1-960.7 (1976)

39. Rhode Island Gen. Laws § 5-19-38 (1976)

40. South Carolina Drug Product Selection Act of 1978, Code §§ 39-24-10 through 39-24-40

41. South Dakota Codified Laws Ann. §§ 36-11-46.1 through 36-11-46.4 (1978)

42. Tennessee Substitution of Equivalent Drug Product Act, Tenn. Code Ann. § 39-2201 (1977)

43. Texas [Health] Code Ann. Tit. 4542, § 12 (1978)

44. Utah Generic Drug Substitution Act, Utah Code Ann. §§ 58-17-29 through 58-17-35 (1977)

45. Vermont Stat. Ann. Tit. 18, § 4605 (1977)

46. Virginia Code Tit. 32.1, §§ 79-88 (1976)

47. Washington Rev. Code Ann. §§ 69.41.100 through 69.41.180 (1977)

48. West Virginia Code § 30-5-12b (1978)

49. Wisconsin Stat. Ann. § 140.90 (1976)

50. Wyoming Generic Drug Substitution Act, Wyo. Stat. §§ 33-24-146 through 33-24-151 (1979)

Amicus Brief

2

MOTION FILED
APR 15 1982

No. 81-1222

IN THE
Supreme Court of the United States

OCTOBER TERM, 1981

UNITED STATES OF AMERICA,
Petitioner,

v.

GENERIX DRUG CORPORATION, *et al.*,
Respondent.

On Writ Of Certiorari To The United States Court Of Appeals For The Eleventh Circuit

MOTION FOR LEAVE TO FILE BRIEF OF AMICUS CURIAE

BRIEF FOR MEDICINE IN THE PUBLIC INTEREST AS AMICUS CURIAE IN SUPPORT OF PETITIONER

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Respondent.

On Writ Of Certiorari To The United States Court Of Appeals For The Eleventh Circuit

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MOTION FOR LEAVE TO FILE BRIEF OF AMICUS CURIAE

Amicus Curiae Medicine in the Public Interest respectfully requests the Court to grant it leave to file a brief as Amicus Curiae in *United States of America* v. *Generix Drug Corporation*, No. 81-1222, currently before this Court. Amicus Curiae wishes to file its brief on behalf of Petitioner United States of America.

Medicine in the Public Interest, Inc. (MIPI) is a non-profit, tax-exempt organization. MIPI was formed in the early 1970s for the purpose of conducting studies, performing analyses, and making evaluations of public and private programs and policies affecting health care in the United States.

Through an interdisciplinary approach, reflecting governmental, academic, medical, industrial, and consumer interests, MIPI has acted as a forum for these disparate interests to identify common ground for dealing with the wide range of health issues that confront modern society. MIPI has organized seminars and conferences on a wide range of health-related topics and has produced publications on such diverse issues as *Dilemmas of Dying: Policies and Procedures for Decisions Not to Treat* (1981); *Mental Illness and the Problem of Boundaries* (1978); and *Human Experimentation* (1976).

MIPI has particularly focused on the complex issues involved in drug research and development, review and approval, and distribution. In recent years MIPI has published five studies in this area alone: *Medical, Legal and Economic Aspects of Drug-Product Selection*[1] (1979); *Drug Abuse, Data Systems and Regulatory Decisions* (1978); *Rights and Responsibilities in Drug Research* (1977); *Postmarking Surveillance of Drugs* (1977); and *Adverse Drug Reactions in the United States: An Analysis of the Scope of the Problem and Recommendations for Future Approaches* (1974). During 1981 MIPI conducted a national conference on new drugs and has produced a draft report from that conference — *Regulating New Drugs: Medical and Policy Issues in the Review and Approval Process.*

MIPI's interest, expertise and experience in issues related to drug policy and MIPI's concern for that policy led MIPI to seek to file an amicus brief in this case.[2]

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[1] Copies of this publication have been lodged with the Clerk of the Court as well as a brochure more fully describing MIPI's activities and listing MIPI's distinguished Board of Directors. The Court's attention is specifically directed to pages 7-18 of *Medical, Legal and Economic Aspects of Drug Product Selection* which contain a discussion of bioequivalence, therapeutic equivalence and bioavailability that is relevant to this case.

[2] By letter dated 2 April, 1982 the Solicitor General consented to the filing of a brief on behalf of Petitioner United States of America. However, in a letter dated 2 April, 1982, counsel for Respondent Generix Drug Corpora-

Amicus Curiae Medicine in the Public Interest will address questions not considered by the parties in this case. Petitioner's petition for a writ of certiorari and Respondent's brief in response thereto both focus on the intricate statutory construction surrounding Section 505 of the Federal Food, Drug and Cosmetic (Act), 21 U.S.C. 355. The central question in those documents, and presumably in the parties' briefs on the merits, is a relatively narrow one: whether the term "new drug" includes "new drug product," specifically generic copies of previously approved pioneer drugs.

MIPI maintains that broad issues of social policy must be brought to this Court's attention as it attempts to resolve the narrow legal issue in this case. The decision in this case will have far-reaching ramifications for the future of health care in this country. The outcome in this case will have a significant impact not only on the generic drug industry but also on the health professions and on their patient/consumers.

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tion informed counsel for MIPI that she was unable to consent to the filing of amicus briefs because she did "not know what the briefs will say or whether any material in the briefs will be objectionable." Counsel indicated that she would determine whether to file an objection after reviewing the briefs submitted by interested amici. It is ironic that counsel is seeking to impose the "pre-marketing clearance" requirement on briefs by amici that she requests this Court to find inapplicable to her client. Copies of these letters have been filed with the Clerk of the Court.

Therefore, Amicus Curiae Medicine In the Public Interest respectfully requests this Court to grant it leave to file an amicus brief in this case.

Respectfully submitted,

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v.

GENERIX DRUG CORPORATION, *et al.*,

Respondent.

BRIEF FOR MEDICINE IN THE PUBLIC INTEREST AS AMICUS CURIAE IN SUPPORT OF PETITIONER

I. AUTHORITY TO FILE

This Amicus Brief is presented to the Court under Rule 36.3 and a motion for leave to file accompanies this Brief.

II. INTEREST OF AMICUS CURIAE

The interest of Amicus Curiae Medicine In The Public Interest is described in the motion for leave to file that accompanies this brief.

III. SUMMARY OF ARGUMENT

The question presented to the Court in this case focuses on a narrow legal issue — whether the definition of a "new drug" in Section 201 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 321(p), applies to entire drug products or only to the active ingredients in those products.

However, it is crucial that this Court be aware of the public policy involved and understand the substantial impact the decision in this case will have on the patient/consumer.

Pre-market review of generic drugs by the Food and Drug Administration (FDA) is mandated by the legislative history and intent of the Federal Food, Drug and Cosmetic Act and its predecessor statutes. The FDA is charged with the responsibility to protect the public from unsafe or ineffective drugs, whether branded or generic.

If Respondent's position is adopted by this Court, allowing untested, unapproved generic drugs to be placed on the market, the patient/consumer will be forced to bear the risk of harm. The parties before the Court admit that generic drugs may differ in bioavailability and in bioequivalence from the FDA approved pioneer drugs which they purport to copy. Yet, Respondent would have this Court adopt an illogically narrow construction of the Food, Drug and Cosmetic Act that would allow these unapproved generic drugs to be sold to and ingested by the American public.

The ultimate result of Respondent's position is two-fold. First, the patient/consumer will be exposed to drugs that may not be effective or, even worse, may be medically unsafe. Second, confidence in generic products generally will be undermined. When the consuming public learns that some generic drugs are being sold without FDA approval, it will not be willing to accept them. This doubt regarding a few generic drugs will undoubtedly affect *all* generic drugs.

Thus, if Respondent were to prevail, the patient/consumer will fall into one or two categories: informed and uninformed. The informed consumer will face two difficult options: whether to accept the generic, thereby saving money, but accepting the risk of ingesting an unsafe or ineffective drug; or refusing the generic to avoid the potential health risk, but thereby failing to

realize potential savings. The uninformed patient will have no such chance as he will continue to buy generic drugs without knowledge of the attendant risk to his health.

Such a choice is incompatible with the public interest and with the public policy behind both the Act and the FDA.

IV. ARGUMENT

A. The Legislative History, Judicial Interpretation, And Explicit Statutory Language Of The Federal Food, Drug, And Cosmetic Act Mandate Pre-market Review And Approval By The Federal Food And Drug Administration Of All Drugs, Branded Or Generic

Section 201 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 321, requires that all drugs and drug products be reviewed and approved by the FDA before being marketed. MIPI does not wish to reiterate the excellent legal analysis contained in the brief filed by Petitioner but wishes to explore the public policy underlying the Act.

The obvious intent of both the current Act and its predecessor statutes has been to protect the American public from unsafe or ineffective products. This concern dates back some seventy-five years to the original Food and Drug Act of 1906.

Shortly after the turn of the century, Dr. Harvey Wiley, Chief of the Division of Chemistry at the Department of Agriculture, became concerned about the toxicity of certain food preservatives. To stimulate legislative action he created what was popularly known as "the poison squad" — twelve volunteers who ate foods liberally treated with toxic preservatives. Studies of the effects these preservatives had on the poison squad led Congress to pass the "Wiley Act" of 1906. *See* Mashaw, "Regulation, Logic and Ideology," *Regulation*, Nov./Dec. 1979, pp. 44-51.

The Federal Food and Drugs Act of 1906, 34 Stat. 768, was essentially a labelling law. The 1906 Act prohibited the manufacture, introduction, shipment, delivery or sale of adulterated or misbranded foods or drugs. The Act deemed a drug adulterated if it differed from recognized standards, except where an explanatory statement was on or in the container. The Act also decreed a drug misbranded if it imitated or used the name of another drug, if some portion of its contents was removed or substituted, if its label failed to state the quantity or proportion of narcotics in the drug, or if it made a false claim of curative or therapeutic effect.

The thrust of the 1906 Act was to protect consumers from the unknown. Note that it prohibited the marketing of a drug that differed from recognized standards. The concern shown in 1906 is readily applicable to the current situation in 1982 whereby Respondent is attempting to market generic products that may differ form the recognized standards of the pioneer drugs approved by the FDA.

In 1938 the Act was radically changed with the passage of a new Food and Drugs Act, 52 Stat. 1052. This legislation was enacted largely as the result of the "Elixir Sulfanilamide Tragedy" of the previous year. The Massengill Company had marketed a newly created sulfa drug, liquid sulfanilamide, without adequately testing it. The preparation contained diethyline glycol and some one hundred people died as a result. *See* "Report of the Secretary of Agriculture on Deaths Due to Elixir Sulfanilamide-Massengill" in C. Dunn, *The Federal Food, Drug and Cosmetic Act — A Statement of Its Legislative Record* (1938) at 1316-1327. It is critical to note that the diethyline glycol added to the liquid sulfanilamide was an inactive ingredient. The parallels between that tragedy and the present situation are unavoidable.

The Food, Drug and Cosmetic Act of 1938 established for the first time the pre-market review and approval process known as

the New Drug Application (NDA) process. The clear thrust of the 1938 statute was to protect the public from drugs that had not been approved by the FDA as being safe.

The legislative purpose and intent of the 1938 Act was reviewed frequently and courts consistently found that the statute was designed to protect the public and as such it should be liberally construed. *See, e.g., United States* v. *Urbuteit*, 335 U.S. 355, 358 (1948); *United States* v. *Dotterweich*, 320 U.S. 277, 280 (1943); *United States* v. *El-O-Pathic Pharmacy*, 192 F.2d 62, 75 (9th Cir. 1951); *Pasadena Research Laboratories* v. *United States*, 169 F.2d 375, 379 (9th Cir.), *cert. denied*, 333 U.S. 853 (1948). As the Ninth Circuit said in *Pasadena Research Laboratories*, "The Act is remedial, and should be liberally construed so as to carry out its beneficient purposes," 169 F.2d at 379.

The 1962 amendments expanded the Act to protect the public from ineffective drugs by requiring all drugs submitted to the FDA for approval to prove both their safety and their efficacy.

These amendments, 76 Stat. 781, were enacted in response to the late Senator Estes Kefauver's lengthy hearings on drugs and the drug industry. These hearings indicated to some that certain pharmaceutical products were yielding "excessive" profits for their manufacturers. Kefauver thus introduced legislation whose thrust was to reduce prices, make generic equivalents available and require that drugs be effective.

The legislation was ultimately enacted largely because of another factor — the outcry about Thalidomide and the deformed babies that resulted from the ingestion of this drug by pregnant women. Thalidomide was, however, marketed mainly overseas and could not have met the then-existing safety standards in this country.

Although the 1962 Amendments were intended to promote price competition and encourage generic drugs, Congress did not seek to exempt generics from the FDA's safety and efficacy review process. S. Rep. No. 1744, 87th Cong., 2nd Sess. 8 (1962), H.R. Rep. No. 2464, 87th Cong., 2nd Sess. 1 (1962). The Senate Report specifically states that anything requiring an NDA — "such as a *new product*" — would be required to meet the efficacy requirements. Reprinted in [1962] U.S. Code Cong. & Ad. News 2884, 2893. The Amendments were designed to strengthen the public's protection, not weaken it.

This Court considered the ramifications of those amendments in a quartet of cases decided in 1973, *Weinberger* v. *Hyson, Westcott and Dunning, Inc.*, 412 U.S. 609 (1973); *CIBA Corporation* v. *Weinberger*, 412 U.S. 640 (1973); *Weinberger* v. *Bentax Pharmaceuticals, Inc.*, 412 U.S. 645 (1973); and *USV Pharmaceutical Corporation* v. *Weinberger*, 412 U.S. 655 (1973). "The Supreme Court, in these four cases, accorded the FDA broad rulemaking powers because of the importance to the public of having safe and effective drugs." Note, New Drug Approval: Lannett, The Drug Lag, and the NDA System, 11 Rutgers Camden L.J. 231, 237 (1980). These cases collectively held that the FDA had the power to determine whether a drug falls within the scope of the Food, Drug and Cosmetic Act and whether substantial evidence has been presented as to its safety and efficacy. In *USV Corporation* v. *Weinberger*, this Court specifically held that the 1962 efficacy amendments applied to generic drugs that existed at the time of those amendments. This Court found that it would be needlessly discriminatory to regulate the products of one manufacturer but not of another, 412 U.S. at 664.

The thrust of the 1962 amendments and the decisions of this Court in the four cases cited *supra* is to expand the protections afforded the public, not restrict them. Respondent's arguments fly in the face of that very thrust. Respondent would have this

Court conclude that Congress intended that the scope of protection would be drastically reduced. However, as this Court wrote in *Weinberger* v. *Hyson, Westcott and Dunning*,

> we cannot construe [the section of the Act defining new drug] to deprive FDA of jurisdiction over a drug which, if subject to FDA regulation, could not be marketed because it had not passed the "substantial evidence" test. To do so "would be to impute to Congress a purpose to paralyze with one hand what it sought to promote with the other."

412 U.S. at 631. Surely Congress did not intend "new drug" to be defined in such a way that FDA review is promoted with one hand yet paralyzed with respect to generic drugs admittedly different in bioavailability and bioequivalence.

The Federal Food, Drug and Cosmetic Act is a remedial statute designed to protect the public and as such it should be given a liberal construction consistent with its purpose of protecting the public health. Courts have repeatedly found that the successive Food and Drug Acts should be liberally construed to protect the public interest. See *United States* v. *An Article of Drug. . . . Bacto-Unidisk*, 394 U.S. 784, 798 (1969); *United States* v. *Naremco*, 553 F.2d 1138, 1141 (8th Cir. 1977); *United States* v. *Diapulse Corporation*, 457 F.2d 24, 28 (2nd Cir. 1972); and *United States* v. *Vitasafe*, 345 F.2d 864, 870 (3rd Cir.), *cert. denied*, 382 U.S. 918 (1965). The public interest in the present case is best served by an interpretation of the statute that recognizes both the intent behind it and the public it serves to protect.

The clear intent of Congress has been to protect the public and to requrie that all drugs, including "drug products," be subject to pre-market clearance. This Court should not allow Respondent to carve out a large exception contrary to that intent. The legislative histories of the Food and Drug Acts, the Congressional hearings related to those Acts, the courts' rulings and the public interest all mandate that generic drugs be re-

quired to pass FDA review before marketing. The purpose of the Act is to subject *all* drugs, including generics, not generally recognized as safe and effective to the pre-market clearance requirements of the Act, *Premo Pharmaceutical Laboratories* v. *United States*, 629 F.2d 795, 805 (2nd Cir. 1980).

This policy is reflected in the latest review of the drug approval process. The Report of the Commission on the Federal Drug Approval Process [3] clearly states that generic drugs should be subject to pre-market clearance. [4]

The draft Commission Report concludes:

> The Commission takes no position on the legal issue raised but does believe that public policy should require such preclearance. The simple fact that two products contain identical amounts of the same active ingredient is not sufficient to protect the public health.

B. Failure To Subject Generic Drugs To Pre-Market Review And Approval Will Place Patient/Consumers At Risk Of Ingesting Unsafe And/Or Ineffective Drugs

If Respondent prevails in this Court, the ultimate result will be the introduction of drugs into commerce that have not been approved as safe and effective by the FDA and possibly have not even been tested for safety and efficacy by the manufacturer. Such drugs, according to Respondent, could be legally sold to an unsuspecting public unaware of the potential dangers involved.

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[3] The non-partisan, interdisciplinary Commission was created by Congress in mid-1981 to review the federal drug approval process and to make recommendations as to how that process could be improved.

[4] The Commission has published a draft report and pages 149-154 specifically address preclearance of generic drugs. Counsel has spoken with the Commission chairmen and has been told that the final report will contain the same conclusions and recommendations concerning generic drug aproval as appears in the draft report. The final report will be presented in late April and Counsel will furnish copies to the Court.

As recounted in the prior decisions in this case, *United States* v. *Generix Drug Corporation*, 654 F.2d 1114 (11th Cir. 1981) and *United States* v. *Generix Drug Corporation*, 498 F.Supp. 288 (S.D. Fla. 1980), Respondent's drugs are generic copies of previously approved pioneer drugs. The active ingredients, termed incipients, are the same in the generic drugs as those in the pioneer drugs they copy. However, the excipients, such as binders, coating, capsules, are not. Excipients represent approximately 90% of the product, *United States* v. *Generix*, *supra*, 654 F.2d at 1115.

The excipients directly affect bioavailability and bioequivalence. Bioavailability is the measure of time it takes for the active ingredients to reach the part of the body they were designed to treat while bioequivalence refers to whether drug products are pharmaceutically equivalent — i.e., whether they have the same therapeutic effect on a particular condition. *See* 21 C.F.R. § 320.1(a), (e) and *Pharmadyne Laboratories, Inc.* v. *Kennedy*, 466 F.Supp. 100, 102, fn. 5, (D.N.J.), *aff'd*, 596 F.2d 568 (3rd Cir. 1979).

Both courts below readily accepted the fact that differences in bioavailability and bioequivalence can affect the safety and efficacy of the generic drug involved. The Eleventh Circuit noted that different excipients may lead to "dumping" whereby all of the active ingredients are dumped into a person's bloodstream. That court further noted that in highly toxic drugs "dumping" may lead to an overdose. 654 F.2d at 1115.

The District Court reviewed the evidence offered by both parties with respect to the drugs involved in this case. One FDA expert "testified that [Respondent's] 'Goldline' products used to treat hypertension are not generally recognized as safe and effective *nor are there any known tests of these products*," 498 F.Supp. at 293. Furthermore, another expert testified, some of the Respondent's products "pose substantial danger because 'dumping' may occur where the formation is not proper, thus

contributing to the possibility of overdose," 498 F.Supp. at 294.

Respondent's expert witness was equally negative about his client's products. He testified that he "assumed" that Generix's Goldline drugs were equivalent to the pioneer drugs but "conceded on cross-examination that he would like some assurances that 'Goldline' products are similar to the brand name products they imitate before the products are marketed," 498 F.Supp. at 294.

The fact that the only expert witness Respondent could find admitted he would like "assurances" before Generix products are marketed certainly justifies doubts about the quality, safety and efficacy of those products.

The fear of harm from these untested drugs is not an idle or a speculative one. The untested drugs Respondent seeks to market without FDA approval claim to meet the standards established by the pioneer drugs which have been approved and are in wide circulation. Respondent's repertoire of unapproved drugs includes copies of products described by the District Court as "widely used" (allopurinol), "one of the most widely used drugs in the United States" (furosemide) and "a combination of drugs [both] widely used" although not in that combination (chlorothiazide with reserpine), 498 F.Supp. at 289-290. Obviously Resondent's products have the potential for reaching large numbers of patient/consumers.

Take, for example, generic furosemide which Respondent wishes to market without FDA clearance. Furosemide is "one of the most widely used drugs in the United States," *supra*, designed as a diuretic and anti-hypertensive. Obviously any widely used heart medicine deserves close scrutiny before being placed on the market. In fact another generic furosemide was believed by the District Court in *Pharmadyne Laboratories, supra*, to pose a potential threat to the public safety.

Furthermore, Medicine in the Public Interest notes the recent manslaughter trial of an Ohio pharmacist for dispensing generic furosemide that had not been approved by the FDA. The generic drug in question was ineffecitve and failed to treat the heart problems of Cleo Schell, 63. Mrs. Schell died of congestive heart failure as the result of the ineffective, unapproved generic. Cleveland Plain Dealer, 15 September, 1981, Akron Beacon Journal, 14 September, 1981.[5]

The harm from untested, unapproved generic drugs can come in three different ways. First, the drug can be unsafe or toxic *per se* and hence present a serious threat to health by its very nature. Second, differences in bioavailability can lead to the "dumping" of too many active ingredients too soon, thus possibly causing an overdose. Third, the drug can be simply ineffective. However, ineffectiveness can lead to failure to treat disease which in turn can lead to sickness, injury or even death. Thus, an ineffective drug can be just as health-threatening or life-threatening as an inherently unsafe one. These concerns are especially acute when the chronically ill are involved. These patients receiving maintenance doses of a drug are particularly susceptible to the danger from an ineffective product.

The legal annals of this country contain a number of examples of unsafe or ineffective drugs sold to the American public. Congress has reacted to such events, be it the "poison squad" (1906 Act), Sulfanilanide Elixir (1938 Act) or Thalidomide (1962 Amendments). There are numerous examples of wide-spread tragedy and wide-spread litigation over products that are inherently dangerous. *See e.g., Ryan* v. *Eli Lilly Co.*, 514 F.Supp. 1004 (D.S.C. 1981) (DES); *Salmon* v. *Parke*

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[5] Counsel is informed that the pharmacist was acquitted of manslaughter in early April of this year. However, the prosecution's inability to prove beyond a reasonable doubt that the druggist contributed to Mrs. Schell's death does not detract from the fact that this unapproved product caused or contributed to her death.

Davis & Co., 520 F.2d 1359 (4th Cir. 1975) (Chloromycetin); *Roginsky* v. *Richardson-Merrill, Inc.*, 378 F.2d 832 (2nd Cir. 1976) (Mer. 29); and *Gottsdanker* v. *Cutter Laboratories*, 182 Cal. App.2d 602, 6 Cal. Rptr. 320 (1960) (polio causing polio vaccine). Yet Respondent seeks to be allowed to market its untested products without FDA approval. Respondent's justification in its brief in opposition to the Government's certiorari petition was to urge that it be allowed to sell its potentially dangerous drugs until or unless Congress acts.

Such positions are contrary to both the letter and spirit of the Act and the very existence of the FDA. The FDA was established to review drugs before they are marketed and to protect the public from any harm. There is tremendous potential for great harm from drugs introduced without testing and without FDA approval. The public interest requires that potentially suspect products be reviewed prior to distribution and sale.

Respondent's concerns about the cost and the delay of the New Drug Application process are not well founded. The FDA has recognized that generic drugs should be reviewed in expedited fashion. Accordingly, generic copies of drugs existing before 1962 may be entitled to use an Abbreviated New Drug Application (ANDA), 21 C.F.R. 314.1. This process, applicable to all pre-1962 drugs for which the FDA has published a Drug Efficacy Study Implementation (DESI) Notice, drastically reduces the time and cost required to obtain FDA approval. Most of Respondent's drugs at issue in this case were and are eligible for the abbreviated NDA process.

Furthermore, the FDA has announced a policy of "paper NDAs," 45 Fed. Reg. 82052 (1980), a similar expedited procedure applicable to generic drugs modeled after pioneer drugs introduced after 1962. Thus, through an ANDA or a paper NDA, generic drugs may be reviewed by the FDA in far less time and at far less cost than their predecessor pioneer drugs.

The draft Report of the Commission on the Federal Drug Approval Process[6] reviewed "the numerous unfortunate instances" involving both generic and pioneer drugs "in which safety problems were caused by factors other than the pure active ingredient," draft Report at 147-148. The Commission concluded that

> the costs in time and money of getting an ANDA approved will be small in comparison to the risks posed by unexamined products on the market, particularly when substition of drug products is actively promoted by federal and state government agencies.

draft Report at 148.

If Respondent were to prevail, who would then determine what is a generic drug? Respondent argues that generic drugs are not new drugs and hence are exempt from FDA review and pre-market clearance. If the Court were to uphold this position, then any manufacturer could claim a product is a generic copy and market it without FDA review. FDA's only recourse would be to challenge the marketing in the Federal courts. Thus, the already overburdened Federal judicial system would be deluged with highly technical, scientific issues, better and more ably resolved by the FDA as the expert agency designated by Congress and recognized by this Court in its 1973 decisions. For this Court to uphold the Respondent's position is to reverse its 1973 decisions and return to the ineffective case-by-case system existing prior to 1973.

Under Respondent's view the FDA would have no power of pre-clearance and hence a highly toxic product could be marketed under the justification that "it's a generic." It is true that if the FDA later discovered and proved that it was not a generic copy or that it was not safe and effective then the FDA would have authority to proceed against the drug. However, the public interest requires that the patient/consumer be protected from

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[6] See footnote 4, *supra*.

potentially unsafe or ineffective drugs before they are placed on the market. A recall of an unsafe product after the fact is time-consuming, unwiedly, often only partially successful in removing the offending product, and usually occurs only after the product's deficiencies have been demonstrated by human tragedy.

Moreover, if generic drugs are allowed to escape FDA pre-market review additional potential health hazards will be raised. Drugs subject to FDA preclearance are also subject to FDA regulations after marketing. FDA related drugs, for example, must meet Good Manufacturing Practices (GMPs). These drugs are subject to manufacturing regulations, record-keeping requirements, and other forms of on-going regulatory compliance. Yet if generic drugs were not required to seek FDA pre-market clearance, they would not be subject to on-going FDA regulation. Such a situation is inherently illogical and is inconsistent with both the spirit and letter of the Act.

The public interest is best served and the public health is best protected by requiring FDA regulation of *all* drugs that are sold to the American public.

C. Failure To Subject Generic Drugs To Pre-Market Review And Approval Will Undermine Acceptance And Utiliziation Of Generic Drugs By Physicians, Pharmacists, And Their Patient/Consumers

Pharmaceutical price competition generally and generic products specifically have been legislatively promoted and encouraged as a matter of public policy. Currently 49 states, the District of Columbia and Puerto Rico have generic substitution laws whereby less expensive generic drugs can be substituted for prescribed branded drugs. These laws are directed towards reducing health care costs to consumers and third party payors including both private health insurance plans and governmental agencies. Cost competition and generic development was one of the motivating factors behind the 1962 amendments to the

Act. The Federal Trade Commission has encouraged individual state generic statutes and in 1979 published a "Model Drug Product Selection Act" as part of an overall review of generic substitution laws, *Drug Product Selection*, Staff Report to the Federal Trade Commission, Bureau of Consumer Protection (1979). This Court has recognized the societal benefit of lower drug prices resulting from the freedom of pharmacists to advertise, *Virginia State Board of Pharmacy* v. *Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 763-764 (1976). *See e.g., Pharmaceutical Society of the State of New York* v. *Lefkowitz*, 586 F.2d 953, 957 (2nd Cir. 1978) recognizing the public benefit of lower prices resulting from generic drugs.

However, much of the public benefit gained from generic substition laws will be lost if generic drugs are allowed to be marketed without FDA review. Fear of untested, unapproved generic products will lead physicans and pharmacists to avoid prescribing and dispensing generic drugs because of their genuine concern for their patients and because of potential product liability/malpractice claims. And patients will refuse generic substitutes because confidence that they are equivalent will be eroded.

Physicians aware of the presence of untested, unapproved generics on the market will likely prescribe only brand name drugs. Since the physician has no practical control over, or knowledge of, which generic product is ultimately dispensed, he or she may well determine to protect his/her patient by requiring only FDA approved brand name products be dispensed. Conceivably, a physician might be held liable for writing a prescription that could be filled by a generic that the doctor knew, or should have known, was a potentially unsafe drug. Whether it be patient-protection or self-protection, doctors are less likely to allow generics to be used when they realize that untested, unapproved generics may be used to fill prescriptions.

The same fear is equally applicable to pharmacists. Those professionals will be equally wary of generic products for the same reasons. Since Federal law forbids any drug or drug package from indicating that the product is FDA approved, 21 U.S.C. 331(l), a pharmacist would be hard-pressed to determine which generic products have been tested for safety and efficacy. Thus, be it out of concern for customers or out of fear of liability, pharmacists will be understandably reluctant to dispense generic products. *See generally* Sonnenreich, "State Substitution Laws: Update on Pharmacist Liability," 3 *U.S. Pharmacist* 15 (1978). The manslaughter trial of the Ohio pharmacist for dispensing an unapproved generic, *supra*, can only heighten those fears.

This concern will ultimately reach the patient/consumer. Knowledgeable patients, aware of the potential risks involved with untested, unapproved generics, will ask their physicians and their pharmacists not to prescribe or dispense them.[7]

If physicians, pharmacists and patients begin to reject generics, then the actions of a few generic manufacturers will adversely affect the entire industry. The presence of some untested generics will tend to drive patient/consumers away from all generics, thus damaging those generic manufacturers who have complied with FDA regulations. A generic manufacturer has emphasized this point in stating that the generic drug market generally would be hurt by the presence of unapproved

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[7] This undesirable situation poses a further problem for the 49 states that have enacted substitution laws. Those states seeking to promote generic substitution would be faced with the question of how to protect their citizens from untested, unapproved generics. Individual states might be then forced to establish their own review mechanisms to determine which generic products are safe and effective. Such a situation would lead to considerable cost, duplication of effort and possible differences in approval between individual states. Common sense and the public interest dictate that drug products be uniformly reviewed by the FDA.

generic drugs. *See Pharmadyne Laboratories, Inc., supra*, 466 F.Supp. at 110-111, fn. 2a.

The key to the success of the generic substitution system is that physicians, pharmacists and patients are able to rely on the FDA's pre-market determination that generic products are equivalent to the pioneer drugs. A lack of professional confidence or a lack of consumer confidence in generic drugs will ultimately erode utilization of generic drugs. State substition laws will lose their impact and the savings those laws were designed to promote will not be realized. In order that the public have confidence in generic products it is essential that *all* such products be subject to FDA pre-market review and regulation.

V. CONCLUSION

Both the intent of Congress and the public interest strongly indicate that this Court should accept Petitioner's argument that the definition of "new drug" includes generic drugs. It is vital that the public be protected from drugs being marketed without a showing beforehand that they are safe and effective as determined by the FDA. It is also important that patient/consumers be able to purchase generic products with the knowledge that those drugs are safe and effective. To decide otherwise would place the patient/consumer in the position of either unknowlingly receiving potentially unsafe or ineffective drugs or consciously refusing to accept any generic drug.

In reviewing the 1938 Food and Drug Act Justice Frankfurter wrote:

> The purposes of this legislation thus touch phases of the lives and health of people, which, in the circumstances of modern industrialism, are largely beyond self protection. Regard for these purposes shall infuse construction of (the 1938 Act) if it is to be treated as a working instrument of

> government and not merely as a collection of English words.

United States v. *Dotterweich*, 320 U.S. 277, 280 (1943).

Those sentiments are equally applicable to the current case. The Federal Food, Drug and Cosmetic Act is not merely a collection of English words, but rather serves as a protection of the public interest and the public health. This protection can last only if all new drugs and all new drug products are required to undergo pre-market review and approval by the Food and Drug Administration.

For the foregoing reasons, Medicine in the Public Interest respectfully requests that this Court reverse the decision of the United States Court of Appeals for the Eleventh Circuit.

Respectfully Submitted,

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UNITED STATES OF AMERICA, PETITIONER

v.

GENERIX DRUG CORPORATION, ET AL.

On Writ of Certiorari to the United States Court of Appeals for the Eleventh Circuit

MOTION FOR LEAVE TO FILE BRIEF AND BRIEF FOR THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION AS AMICUS CURIAE

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MOTION OF THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION FOR LEAVE TO FILE BRIEF AS AMICUS CURIAE

The Pharmaceutical Manufacturers Association (PMA) hereby moves, pursuant to Rule 36.3 of the Rules of this Court, for leave to file the attached brief as *amicus curiae* urging reversal. The United States has consented to the filing of the brief; respondents have withheld their consent.

PMA is a voluntary nonprofit association of 149 companies engaged in the discovery, development, manufacture and marketing of prescription drugs, medical devices and diagnostic products. Leave is sought to file a brief as *amicus curiae* because this case presents an im-

portant issue as to the coverage of the Federal Food, Drug, and Cosmetic Act, the basic regulatory statute governing the pharmaceutical industry. PMA traditionally has acted as spokesman for its members on important questions of federal law affecting their interests.[1]

PMA member companies have created and introduced, at great expense and scientific effort, the majority of the "pioneer" or brand-name prescription drugs copied by manufacturers of "generic" or "me-too" drugs, which are marketed as substitutes for the brand-name products. In addition, many PMA members themselves market "me-too" versions of prescription drugs introduced by others. The decision below would exempt all "me-too" prescription drugs from the "new drug" approval requirements of the Federal Food, Drug, and Cosmetic Act, and thus allow "me-too's" to reach the market with no advance scrutiny by the Food and Drug Administration, even though there is no assurance that they are—and even though they sometimes are not in fact—therapeutically equivalent in safety or effectiveness either to the copied brand-name drugs or to competing "me-too" versions that have received FDA approval. PMA members therefore have a substantial stake in the outcome of this litigation.

Under the Federal Food, Drug, and Cosmetic Act, pharmaceutical manufacturers seeking marketing approval from the Food and Drug Administration for "new drugs" are required to submit in advance highly detailed new drug applications (NDAs) containing scientific data that establish, under a rigorous evidentiary standard, the safety and effectiveness of their products. Such data

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[1] PMA has in the past filed briefs as *amicus curiae* in cases in this Court involving the impact of federal law on the pharmaceutical industry. *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973) and companion cases; *Diamond v. Chakrabarty*, 447 U.S. 303 (1980); *Dawson Chem. Co. v. Rohm & Haas Co.*, 448 U.S. 176 (1980); *Inwood Labs., Inc. v. Ives Labs., Inc.*, Nos. 80-2182 and 81-11, *pending*.

must include full reports of clinical investigations, a full statement of the composition of the drug, including both active and inactive ingredients, and a full description of the methods used in its manufacture. For many "me-too" drugs abbreviated procedures are available under FDA regulations.[2] In all cases, however, FDA approval is required before a "new drug" may be marketed.

A "me-too" prescription drug purports to contain the same active ingredient as the "pioneer" drug for which it is offered as a substitute. But almost invariably it contains different inactive ingredients, known as excipients —which are added to form a tablet or as capsule coating, coloring or flavoring—and is manufactured under different methods and conditions. Because of these differences, affecting such things as solubility and rate of absorption into the bloodstream, many "me-too" prescription drugs are not therapeutically equivalent to the approved "pioneer" drugs they imitate, and may be unsafe or ineffective. The decision below, however, would permit manufacturers and distributors of "me-too" prescription drugs to market their products without any prior FDA approval or scrutiny whatsoever to assure that minimum standards of safety and effectiveness are met.

The court of appeals' interpretation of the Act, in disregard of its plain language, is not only erroneous but also poses a serious risk of injury to the public health. This in itself is a matter of concern to PMA's members, because the business of the pharmaceutical industry is protection of the public health.

In addition, the decision below threatens to distort competition in the pharmaceutical industry. Physicians often authorize substitution of "me-too" drugs for brand-name drugs on an assumption of therapeutic equivalence—an assumption that may be contrary to fact. Therapeutic failures have sometimes resulted. Such failures may well

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[2] *See* Pet. 18-19 & n.30.

be blamed on the active ingredients and thus cause physicians to prescribe different drugs without warrant. Not only would patients thereby be deprived of appropriate therapy, but legitimate sales would be diverted both from the "pioneers" and from competing "me-too" drugs—including those marketed by PMA members—that have been reviewed and approved by FDA as safe and effective. PMA members would thus be directly and adversely affected by a regulatory regime that allows unapproved "me-too" prescription drugs to be marketed as substitutes for approved "pioneer" drugs with only the "me-too" manufacturer's say-so that its drug is equally safe and effective.

The briefs and arguments of the parties will necessarily and properly focus on the particular facts and narrow issue presented by this case. PMA's brief, on the other hand, focuses on the broad potential public health consequences of allowing the court of appeals' decision to stand. This is a matter that warrants consideration by the Court in its resolution of the instant case.

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On Writ of Certiorari to the United States Court of Appeals for the Eleventh Circuit

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BRIEF FOR THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION AS AMICUS CURIAE

INTEREST OF AMICUS CURIAE

The Pharmaceutical Manufacturers Association (PMA) is a voluntary nonprofit association of 149 companies engaged in the discovery, development, manufacture and marketing of prescription drugs, medical devices and diagnostic products. PMA has a substantial interest in this case because it presents an important question as to the coverage of the Federal Food, Drug, and Cosmetic Act of 1938, as amended, 21 U.S.C. §§ 301 *et seq.*, the basic regulatory statute governing the pharmaceutical industry.

The decision below would exempt all "generic" or "me-too" prescription drugs from the "new drug" approval requirements of the Act. Its effect is to allow "me-too's" to reach the market with no advance scrutiny whatso-

ever by the Food and Drug Administration to assure that they meet minimum standards of safety and effectiveness.

The court of appeals' interpretation of the Act is not only erroneous but poses a serious risk of injury to the public health. In addition, it threatens to distort competition in the pharmaceutical industry. As explained more fully in PMA's motion for leave to file this brief, therapeutic failures resulting from the substitution of unsafe or ineffective "me-too" prescription drugs may be blamed on the active ingredients they purportedly have in common with the "pioneer" drugs for which they have been substituted, most of which were created and introduced by PMA members. This may cause some physicians to lose confidence in the "pioneer" drug itself, and in other cases to steer away from "generic" substitutes as a class, including "generics" that FDA has in fact approved as safe and effective. Both as "pioneer" prescription drug manufacturers and as important participants in the "generic" segment of the pharmaceutical industry, therefore, PMA members have a substantial stake in the outcome of this case.

SUMMARY OF ARGUMENT

I.

The court of appeals held that inactive ingredients and manufacturing techniques are irrelevant to whether a prescription drug is a "new drug" requiring premarket approval by the Food and Drug Administration. But both the scientific literature and a spate of recently decided cases show that these aspects of a prescription drug can be crucial determinants of its safety and effectiveness. Indeed, the Federal Food, Drug, and Cosmetic Act of 1938—and particularly its "new drug" approval requirement—was passed in direct response to the death of 100 persons the previous year in the "Elixir of Sulfanilamide" tragedy, which stemmed from the marketing of a "generic" drug combining a proven active ingredient in an untried liquid

vehicle (diethylene glycol, or antifreeze) presumed, incorrectly, to be harmless.

The effect of the decision below is to allow "generic" versions of previously approved prescription drugs to be marketed and dispensed to patients as substitutes, solely on the "generic" manufacturer's say-so that its drug is equally safe and effective. Absent premarket review by FDA, the government must utilize inefficient after-the-fact remedies to deal with unsafe or ineffective "generic" prescription drugs. This result is contrary to the fundamental purpose of the Act's "new drug" provisions, which is "to protect the public from danger to human life arising from the use of unsafe and ineffective drugs by assuring that *before* any drug is marketed it will have been carefully reviewed by FDA experts." *Premo Pharmaceutical Laboratories, Inc. v. United States*, 629 F.2d 795, 802 (2d Cir. 1980) (emphasis added).

II.

The plain language of the statute neither requires nor permits the crabbed and self-defeating construction placed upon it by the court of appeals. Properly parsed, the statutory definitions of "drug" and "new drug" clearly encompass specific drug products and not just their active ingredients. The decision below, moreover, requires reading the term "new drug" differently in the two separate but interdependent sections of the statute in which it principally appears, contrary to well-established principles of construction. Nor does the statute's contemplation that "new drugs" ultimately may become "old drugs" make it necessary to ignore inactive ingredients and manufacturing techniques in determining "new drug" status, as the court of appeals thought; "general recognition" of a prescription drug's safety and effectiveness does not require widespread knowledge of its exact formulation or techniques of manufacture, but only of the scientific studies that have been performed on the drug and that show it to be safe and effective.

ARGUMENT

I. THE DECISION BELOW SIGNIFICANTLY IMPAIRS FDA'S ABILITY TO PROTECT THE PUBLIC HEALTH.

A. The importance of this case from a public health standpoint cannot be doubted. "Because manufacturing techniques vary," as the court below recognized, "generic drug products often combine an active ingredient that is generally recognized as safe and effective and excipients that are unique to the individual manufacturer." 654 F.2d at 1115, Pet. App. 3a. Such differences in excipients and manufacturing techniques, under the court of appeals' view, are irrelevant to the issue of "new drug" status. But they are by no means irrelevant to determinations of therapeutic equivalence or of safety and effectiveness. *See, e.g., Premo Pharmaceutical Laboratories, Inc. v. United States*, 629 F.2d 795, 805 (2d Cir. 1980) (*"Premo I"*). The "Elixir of Sulfanilamide" tragedy, which involved more than 100 deaths and led directly to passage of the 1938 Act, stemmed from the marketing, without FDA preclearance, of a "me-too" drug combining a proven active ingredient with a new inactive ingredient (diethylene glycol, or antifreeze) presumed—incorrectly—to be harmless. *See United States v. Premo Pharmaceutical Laboratories, Inc.*, 511 F. Supp. 958, 962 (D.N.J. 1981) (*"Premo II"*).[1]

Differences in excipients and modes of manufacture indisputably affect the bioavailability and bioequivalence of drugs:[2]

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[1] *See also* Pet. 16 & n.25 and authorities cited therein.

[2] Bioavailability is the rate and extent to which the active ingredient is absorbed from the drug product and becomes available at the site of drug action. Bioequivalence means that the rate and extent of absorption of two drug products are sufficiently equal that the products may be expected to behave the same way in a clinical situation. *See Premo II, supra*, 511 F. Supp. at 962-63, 980-81; *Pharmadyne Laboratories, Inc. v. Kennedy*, 466 F. Supp. 100, 102 n.5 (D.N.J.), *aff'd on other grounds*, 596 F.2d 568 (3d Cir. 1979).

> There are many factors that can affect a drug's bioavailability. Among these are the particle size and crystalline form of the active ingredient; the choice of inactive ingredients (excipients), such as binders and fillers; the facilities and controls used in the manufacture and processing of the drug; and the environmental conditions during manufacture and storage.

Premo II, supra, 511 F. Supp. at 963.[3] Variations in any of these factors may preclude therapeutic equivalence between a "pioneer" and "me-too" prescription drug and lead to toxicity and therapeutic failure when the "me-too" drug is dispensed as a substitute. *See Pharmadyne Laboratories, Inc. v. Kennedy*, 466 F. Supp. 100, 110 (D.N.J.), *aff'd on other grounds*, 596 F.2d 568 (3d Cir. 1979). "When two different drug products are to be used interchangeably in the treatment of illness, it can be critical that the products are bioequivalent—that is, that there be no significant difference in the products' bioavailability." *Premo II, supra*, 511 F. Supp. at 963.

The scientific literature is replete with evidence that many generic prescription drugs differ in bioavailability from the "pioneer" products they imitate and that these differences often affect safety or effectiveness.[4] Such instances have been further documented in recent litigation.

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[3] The district court there, on the basis of an exhaustive evidentiary record, spelled out in detail why each of the factors listed may significantly affect the bioavailability of a drug. *Id.* at 964-65, 980-85.

[4] *E.g.*, Office of Technology Assessment, U.S. Congress, *Drug Bioequivalence* 11-14 (1974); D. Chodos & A. DiSanto, *Basics of Bioavailability* (Upjohn Co., 1974); Rubinstein & Eastwood, *The Effect of Lubricant Type and Concentration on the Bioavailability of Furosemide from 40 Mg. Tablets*, 30 J. Pharm. & Pharmacol. 12 (Supp. 1978); DeSante *et al.*, *Generic Propoxyphene: Need for Clinical Bioavailability Evaluation*, 66 J. Pharm. Sci. 1713 (1977); Kramer *et al.*, *Digoxin Bioavailability: Evaluation of a Generic Tablet and Proposed FDA Guidelines*, 66 J. Pharm. Sci. 1720 (1977); Azarnoff & Huffman, *Therapeutic Implications of Bioavailability*, 16 Ann. Rev. Pharm. & Tox. 53 (1976).

—*SK&F, Co. v. Premo Pharmaceutical Laboratories, Inc.*, 625 F.2d 1055 (3d Cir. 1980), involved a "me-too" version of Dyazide®, an oral diuretic widely prescribed for hypertension. Premo's "me-too" product, according to FDA, possessed a sevenfold greater bioavailability than the "pioneer" drug and "could cause a toxic buildup of potassium." *Id.* at 1061 n.4.

—In *Premo II, supra*, 511 F. Supp. at 994-99, the court found as to five other prescription drugs that any bioavailability differences between the "pioneer" product and "me-too" generic versions would have potentially serious adverse consequences:

Drug	Condition Treated	Potential Adverse Consequences of Varying Bioavailability
trifluoperazine	psychosis	involuntary movements causing permanent injury
allopurinol	gout	urinary failure
doxylamine succinate	nausea due to pregnancy	dizziness, headaches, drowsiness
hydroxyzine pamoate/ hydroxyzine hydrochloride	emotional distress, psychomotor agitation	drowsiness, tremors, convulsive episodes
chlorthalidone	hypertension and edema	cardiac toxicity, leading to death

—*Premo I, supra*, concerned Premo's "me-too" version of insulase, a prescription drug used to reduce blood sugar in diabetics. The record in *Premo I*, Appendix at 100, contains evidence that Premo's form of that drug was ineffective.

—In *Pharmadyne Laboratories, Inc. v. Kennedy, supra*, the court relied on evidence that Pharmadyne's "me-too" version of furosemide, another widely-prescribed antihypertensive drug, was "very likely . . . ineffective" at the prescribed dosage of the "pioneer" product (Lasix®) and was "a potential hazard in the marketplace" absent

"further proof of *in vivo* bioavailability." 596 F.2d at 572 n.8 (quoting 466 F. Supp. at 110).[5]

B. While differences in inactive ingredients and modes of manufacture can affect safety and effectiveness, as shown above, the court of appeals' decision permits "me-too" prescription drugs to be introduced and marketed without any prior FDA scrutiny whatsoever, so long as a "pioneer" drug containing the same active ingredient has been approved by FDA as safe and effective. This interpretation creates a major gap in the protections afforded by the Act. "The purpose of the Act, as enacted in 1938 and amended by Congress in 1962, is to protect the public against danger to human life arising from the use of unsafe and ineffective drugs by assuring that *before* any drug is marketed it will have been carefully reviewed by FDA experts." *Premo I, supra*, 629 F.2d at 802 (emphasis added). *See Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 612 (1973). But if the decision below is allowed to stand, a "me-too" prescription drug manufacturer would be able "to substitute its opinion regarding the safety or effectiveness of a drug for that of the FDA . . . ." *Premo I, supra*, 629 F.2d at 802.

Absent premarketing review by FDA, the government must utilize post-marketing remedies such as injunction suits like this one, 21 U.S.C. § 332, or lot-by-lot seizure actions, 21 U.S.C. § 334, to deal with "me-too" drugs that are unsafe or ineffective. Such remedies are notably inefficient. Indeed, there may be a time lag of up to six months before FDA is even aware that a particular "me-too" drug exists and has been placed on the market. *Premo II, supra*, 511 F. Supp. at 976-77; *Pharmadyne Laboratories, supra*, 466 F. Supp. at 105; *see* 21 U.S.C. § 360(j)(2). The risks to the public health under such a regime are evident; FDA may be unaware of an unsafe or ineffective "me-too" prescription drug "until it is

[5] In a press release issued March 30, 1979, FDA warned of the grave harm that unapproved generic furosemides then marketed could cause, and reported four serious incidents.

too late to protect the public." *Premo II*, *supra*, 511 F. Supp. at 977.

To be sure, the court of appeals' construction of the statute would spare "me-too" manufacturers a regulatory burden that some may find onerous, and in that way facilitate new entry into the market for a particular drug. But "deregulation" and "regulatory reform" are for Congress and the agencies, not the courts, to accomplish. And certainly, the courts should be slow to put a crabbed construction on regulatory legislation, such as the "new drug" premarket approval requirement, that "touch[es] phases of the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self-protection." *United States v. Dotterweich*, 320 U.S. 277, 280 (1943). Congress' decision to provide the protection of a premarket approval requirement for new drugs was a wise one, not to be undermined in the name of "competition" as the decision below would do.

II. THE TERMS OF THE FOOD, DRUG, AND COSMETIC ACT CLEARLY SUBJECT "ME-TOO" VERSIONS OF PREVIOUSLY-APPROVED PRESCRIPTION DRUGS TO THE ACT'S PREMARKET APPROVAL REQUIREMENT.

To be sure, it is not enough that FDA preclearance of "me-too" prescription drugs would be "good public policy"; undeniably, as the court below stated, "[t]he judicial branch may not legislate to fill perceived voids in public policy." 654 F.2d at 1119-20, Pet. App. 14a. But it is the court of appeals, not FDA, that reads the Act erroneously and fails to respect its plain language.

A. Neither the term "new drug" nor the words "[a]ny drug" in section 201(p), which defines "new drug," [6]

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[6] Section 201(p), 21 U.S.C. § 321(p), provides in pertinent part:

The term "new drug" means—

(1) Any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by

convey on their face the limited meaning assigned by the court of appeals, namely, that "new drug" means only the active ingredient of a drug product and not a drug product itself. In fact, section 201(p) defines "new drug" as "[a]ny drug . . . *the composition of which* is not generally recognized . . . as safe and effective"—language inconsistent with the view that "any drug" means "any active ingredient" (emphasis added).

The definition of "drug" in section 201(g)(1), 21 U.S.C. § 321(g)(1), is likewise in conflict with the court of appeals' position.[7] At the least, clause (B) of that section, which covers "*articles intended for use* in the diagnosis, cure, mitigation, treatment, or prevention of disease" (emphasis added), on its face encompasses specific drug products, not just their active ingredients. Nor can it be argued that "articles" in clause (B) means only

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scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . or

(2) Any drug . . . the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

[7] Section 201(g)(1), 21 U.S.C. § 321(g)(1), provides in pertinent part:

(1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C) of this paragraph; but does not include devices or their components, parts, or accessories.

active ingredients, because clause (D) refers to "articles intended for use *as a component of any article specified in clauses (A), (B) or (C)*" (emphasis added). Plainly, the use of the term "component" in this final clause makes no sense unless clauses (A) through (C) include drug products, rather than merely individual ingredients.

A further flaw in the court of appeals' interpretation is that it requires assigning two different meanings to the same term, "new drug," in the same statute.[8] According to the court, "new drug" in section 201(p), the definitional section, means only the active ingredient of a drug product. 654 F.2d at 1120, Pet. App. 15a. But the same term in section 505 of the Act, 21 U.S.C. § 355, the operational section dealing with new drug applications, necessarily encompasses drug products because it requires each applicant to submit "a full list of the articles used as components of such drug," "a full statement of the composition of such drug," and "a full description of the methods" of manufacture.[9] As the Court has ex-

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[8] "It is well established that our task in interpreting separate provisions of a single Act is to give the Act 'the most harmonious, comprehensive meaning possible' in light of the legislative policy and purpose." *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 631-32 (1973) (quoting *Clark v. Finanz-Korp.*, 332 U.S. 480, 488 (1947)).

[9] Sections 505(a) and (b), 21 U.S.C. §§ 355(a)-(b), provide as follows:

> (a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) of this section is effective with respect to such drug.
>
> (b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (2) a full list of the articles used as components of such

plained, "an NDA covers a particular product or products that it names. . . . Section 505, in other words, addresses itself to drugs as individual products." *USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655, 664 (1973).

This Court has also held, moreover, that "the reach of scientific inquiry" under sections 201(p) and 505 is the same. *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 653 (1973). If inactive ingredients and manufacturing methods were of concern to Congress in connection with the introduction of "pioneer" prescription drugs, there is no reason to believe that Congress was wholly unconcerned with these same matters in the case of "me-too" drugs. *Pharmadyne Laboratories, Inc. v. Kennedy*, 466 F. Supp. 100, 103-04 (D.N.J.), *aff'd on other grounds*, 596 F.2d 568 (3d Cir. 1979); *United States v. Premo Pharmaceutical Laboratories, Inc.*, 511 F. Supp. 958, 968-69 (D.N.J. 1981).

Nor is there merit to the court of appeals' rationale that the exclusion of drugs "generally recognized as safe and effective" from the "new drug" definition would be a dead letter "[i]f 'new drug' refers to the drug product as opposed to the active ingredient." 654 F.2d at 1117, Pet. App. 7a. This exclusion is designed to permit drugs on the market to "drop out" of "new drug" regulation at some point after they have "mustered the requisite scientifically reliable evidence of effectiveness . . . ." *Weinberger v. Hynson, Westcott & Dunning, Inc.*, *supra*, 412 U.S. at 631. The court of appeals surmised that because information relating to the safety and effectiveness of a

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drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug.

drug product, such as manufacturing techniques and the precise formulation, are "closely guarded trade secret[s]" not revealed to the scientific community, a drug product can never qualify under the "generally recognized" exclusion and would always remain a "new drug." 654 F.2d at 1117, Pet. App. 7a. But a factual premise for that supposition is wrong. If a drug product is on the market and thus readily available, it is simply not necessary that the scientific community know its precise formula or mode of manufacture in order to conduct and evaluate the requisite scientific investigations.[10]

Accordingly, a prescription drug product is a "new drug" under the Act, subject to FDA preclearance, unless it falls within the "very narrow" exclusion for drugs "generally recognized as safe and effective." *Premo Pharmaceutical Laboratories, Inc. v. United States*, 629 F.2d 795, 802 (2d Cir. 1980). Generix's drugs in this case, like the vast majority of "me-too" prescription drugs,[11] clearly do not meet the "generally recognized" standard.[12]

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[10] The court below also accorded great weight to Congress' goal in 1962 of facilitating the use of less expensive generic drugs. 654 F.2d at 1118-19, Pet. App. 10a-12a. But it is highly unlikely that the court's interpretation would advance that goal. "Since doctors can disavow generic substitution when writing a prescription, it should be obvious that they will have greater motive to do so if they realize that their patient may be getting a medication that the FDA has not approved." *Pharmadyne Laboratories, supra*, 466 F. Supp. at 106. In any case, nothing in the legislative history of the 1962 amendments remotely suggests that Congress intended to encourage the use of generic prescription drugs at the risk of serious injury to the public health.

[11] *See, e.g., Premo I, supra*, 629 F.2d at 804, 805; *Premo II, supra*, 511 F. Supp. at 973-75.

[12] The district court found that six of the eight Generix drug products at issue "have not been tested" and are not "generally recognized among [qualified] experts" as safe and effective. 498 F. Supp. at 290, Pet. App. 20a. As to the two remaining drugs, the district court did not make a contrary finding but rather held that the government failed to establish a "reasonable possibility

CONCLUSION

The judgment of the court of appeals should be reversed.

Respectfully submitted,

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that differences between the copied drug product and the generic drug product affect the safety and effectiveness of the generic drug product." *Id.* at 293, Pet. App. 28a. It was surely erroneous, however, for the court to determine in the first instance whether drug products might or might not in fact be safe and effective; its function is appropriately limited to determining the state of scientific opinion—whether such products are "generally recognized" by experts to be safe and effective. *Premo I, supra*, 629 F.2d at 803-04; *AMP, Inc. v. Gardner*, 389 F.2d 825, 831 (2d Cir.), *cert. denied*, 393 U.S. 825 (1968).

Amicus Brief

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1981

UNITED STATES OF AMERICA,
Petitioner,

v.

GENERIX DRUG CORPORATION, *et al.*,
Respondents.

On Writ of Certiorari to the United States Court of Appeals For The Eleventh Circuit

MOTION FOR LEAVE TO FILE BRIEF *AMICUS CURIAE* AND BRIEF *AMICUS CURIAE* ON BEHALF OF THE PROPRIETARY ASSOCIATION

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MOTION FOR LEAVE TO FILE BRIEF *AMICUS CURIAE* ON BEHALF OF THE PROPRIETARY ASSOCIATION

The Proprietary Association, pursuant to Rule 36.3 of the Rules of this Court, hereby respectfully moves this Court for leave to file an *amicus curiae* brief in this case in support of neither party. Written consent to the filing of such brief has been obtained from the petitioner, but withheld by the respondents.

The Proprietary Association is a 101-year-old national trade association whose active member companies manufacture and distribute the vast majority of the Nation's supply of over-the-counter medicinal preparations ("OTC drugs"). The Proprietary Association does not represent the interests of manufac-

turers of prescription drugs. OTC drugs are intended for use in self-medication of minor ailments and are legally purchased by the consumer without a prescription.

This case concerns the allegedly unlawful marketing of generic prescription drugs by respondents. The injunctive relief granted by the district court below covered certain of those generic prescription drugs distributed by respondents. The Proprietary Association takes no position on the merits of the question presented by the petitioner here. The Proprietary Association's interest in this case derives solely from the fact that respondents, in their brief dated February 3, 1982 opposing the United States of America's ("Government") petition for a writ of certiorari, have sought to interpose issues regarding the legality of the present regulation of OTC drugs by the Food and Drug Administration ("FDA"). While the Government has framed the question presented as concerning premarketing approval by the FDA of prescription drug products, respondents seek to broaden the scope of the proceeding beyond that question and beyond the record in this case. Accordingly, The Proprietary Association seeks to express its views on behalf of its membership.

Since 1972, The Proprietary Association and its members have cooperated at very substantial expense in a comprehensive review of OTC drugs by the FDA, denominated the OTC Drug Review. *See* 21 C.F.R. Part 330 (1981). This program is massive in nature, and is designed to confirm that the numerous OTC drugs available on the market are generally recognized by experts as safe and effective under recommended or suggested conditions for use and are not misbranded. Ten years after the OTC Drug Review commenced, in a case in which no factual or legal record has been developed relating to OTC drug regulation or scientific determinations of general recognition of OTC drugs, arguments are being presented to this Court which challenge that complex administrative proceeding. To the extent that respondents divert attention from generic prescription drugs to much different questions regarding OTC drugs, the members of The Proprietary Association may be substantially and directly affected in their conduct of the business of manufacturing and distributing OTC drugs.

These considerations raise matters distinct from the interests of the parties now before the Court. The Proprietary Association thus believes that an *amicus* brief can assist in clarifying and resolving the issues presented to the Court.

Respectfully submitted,

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21 C.F.R. § 330.1(a)-(j) (1981) 6
21 C.F.R. Part 331 (1981) 11
21 C.F.R. Part 332 (1981) 11
21 C.F.R. Part 361 (1981) 11
37 Fed. Reg. 9,464 (1972) 5
46 Fed. Reg. 47,730 (1981) 6

RULES:

Rules of the United States Supreme Court—Rule 21.1(a) 8

MISCELLANEOUS:

Durham-Humphrey Amendments of 1951: Hearings on S.1552 Before the Kefauver Subcomm. of the Senate Comm. on Labor and Public Welfare, 82d Cong., 1st Sess. (1951) 10
H. REP. NO. 700, 82d Cong., 1st Sess. (1951) 10
S. REP. NO. 946, 82d Cong., 1st Sess. (1951) 10

IN THE

Supreme Court of the United States

OCTOBER TERM, 1981

No. 81-1222

UNITED STATES OF AMERICA,
Petitioner,

v.

GENERIX DRUG CORPORATION, *et al.*,
Respondents.

On Writ of Certiorari to the United States Court of Appeals For The Eleventh Circuit

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BRIEF *AMICUS CURIAE* ON BEHALF OF THE PROPRIETARY ASSOCIATION

INTEREST OF AMICUS CURIAE

The Proprietary Association is a 101-year-old national trade association whose active member companies manufacture and distribute the vast majority of the Nation's supply of over-the-counter medicinal preparations ("OTC drugs"). OTC drugs are intended for use in self-medication of minor ailments and are legally purchased by the consumer without a prescription.

This case concerns the allegedly unlawful marketing of generic prescription drugs by respondents. The injunctive relief granted by the district court below covered certain of those generic prescription drugs distributed by respondents. The Proprietary Association's interest in this case derives solely from the fact that respondents, in their brief dated February 3, 1982

opposing the United States of America's ("Government") petition for a writ of certiorari, have sought to interpose issues regarding the legality of the present regulation of OTC drugs by the Food and Drug Administration ("FDA"). While the Government has framed the question presented as concerning premarketing approval by the FDA of prescription drug products, respondents seek to broaden the scope of the proceeding beyond that question and beyond the record in this case. Accordingly, The Proprietary Association, which traditionally has acted as spokesman for the OTC drug industry, here seeks to express the position of its members who may be substantially and directly affected in their conduct of the business of manufacturing and distributing OTC drugs.

OPINIONS BELOW

The opinion of the United States Court of Appeals for the Eleventh Circuit[1] is reported at 654 F.2d 1114 (1981).

The decision of the district court is reported at 498 F. Supp. 288 (S.D. Fla. 1980).[2]

JURISDICTION

The judgment of the court of appeals was entered on September 4, 1981. On March 1, 1982, this Court granted the petition for a writ of certiorari filed by the Government. Jurisdiction of this Court rests on 28 U.S.C. § 1254(1).

STATUTES AND REGULATIONS INVOLVED

The statutory provisions and regulations referenced below are set forth in the accompanying Appendix ("App.").

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[1] This case was decided by Unit B of the Fifth Circuit which, on October 1, 1981, became the Eleventh Circuit.

[2] The complete texts of the court of appeals and district court decisions appear in Appendices A and C to the Petition For a Writ of Certiorari ("*Cert. Pet.*") filed in December, 1981 by the United States of America.

STATEMENT

This Case

1. In the district court below, the Government alleged that certain generic formulations of prescription drugs distributed by defendant Generix Drug Corporation ("Generix") were in fact "new drugs" without approved new drug applications ("NDAs") in violation of the premarketing clearance requirements of section 505(a) of the Federal Food, Drug, and Cosmetic Act (the "Act"), *as amended,* 21 U.S.C. § 355(a) (1976).[3] Having found that Generix shipped its generic prescription drug products in interstate commerce without having filed for NDAs, the district court stated that "the only remaining task is to determine whether *these specific generic drug products* are 'new-drugs'." 498 F. Supp. at 290 (emphasis added). After considering the evidence presented and applicable law, the court granted a preliminary injunction with respect to Generix's prescription drug products containing six specific active ingredients, and denied relief as to prescription drug products containing two other active ingredients. *Id.* at 294. Nowhere did the district court address OTC drugs or the legality of FDA regulation with regard to them.

2. None of the expert testimony presented to the district court below addressed the characteristics of the active or inactive ingredients, manufacturing processes, or sale of over-the-counter ("OTC") drugs, *i.e.* medicinal preparations which, unlike prescription drugs, are intended for self-medication of minor ailments and are legally purchased by the consumer without a prescription. Nor was any record developed regarding the nature and history of the FDA's on-going regulatory review of OTC drugs under special rulemaking procedures adopted in 1972 (the "OTC Drug Review" or "Review"). *See* 21 C.F.R. Part 330 (1981). (App. 1b-25b).

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[3] Section 505(a) prohibits any person from introducing into interstate commerce any "new drug" that has not received prior FDA approval. (App. 5a). The term "new drug" is defined by section 201(p) of the Act, 21 U.S.C. § 321(p), to mean any drug that is not "generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof," and has not been used to a material extent or for a material time under other than experimental conditions. (App. 1a).

3. The court of appeals decision, vacating the district court's preliminary injunction and remanding with instructions to dismiss, similarly contained no discussion of OTC drugs or the OTC Drug Review, or gave any indication that the legality of FDA regulation of OTC drugs was at issue.

4. In the petition for writ of certiorari, the Solicitor General presents the following question to this Court:

> Whether a *prescription* drug product—even though potentially unsafe or ineffective—is exempt from the requirement of premarketing approval by FDA merely because it contains the same active ingredient as another drug that has received FDA approval or that is generally recognized as safe and effective [4] (emphasis added).

5. In their brief in opposition, respondents state the question quite differently:

> Whether all generic drug products, *including over the counter products,* require premarketing approval by the FDA when they contain active ingredients which are generally recognized as safe and effective [5] (emphasis added).

In their brief opposing certiorari, respondents claim that, contrary to the Solicitor General's phrasing of the question presented, OTC drugs are at issue, and furthermore that acceptance of the Government's view—that "new drug" means new drug product or formulation—would render the FDA's approach toward OTC drugs under the OTC Drug Review "illegal." *Opp. Br.* at 3 n.5.

The OTC Drug Review

In 1972, the FDA initiated the OTC Drug Review to evaluate the safety and effectiveness of the ingredients and the adequacy of the labeling of all of the FDA-estimated 100,000

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[4] *Cert. Pet.* at (I).

[5] Respondents' Brief in Opposition ("*Opp. Br.*") filed February 3, 1982.

to 500,000 nonprescription or OTC medicines. The regulations governing this Review were subject to public notice and comment before being implemented. *See* 37 Fed. Reg. 9,464-75 (1972). The OTC Drug Review has been a mammoth project, undertaken at a cost of many millions of dollars to the Federal government and substantial additional millions to the OTC medicines industry. Approximately 20,000 volumes of data have been submitted by the industry to advisory review panels of the FDA. For ten years, the Review has progressed under comprehensive FDA supervision and with extensive industry involvement. It is not a short-term proceeding designed to address a few isolated drug products distributed by a particular drug firm. Rather, hundreds of OTC manufacturers and many thousands of OTC drugs have been subjected to scientific review.

In statutory terms, the OTC Drug Review represents an effort by the FDA, in an exercise of informed, administrative discretion, to confirm that myriad OTC drugs, many of which have been marketed for decades with no safety problems, are not "new drugs" under section 201(p) of the Act, 21 U.S.C. § 321(p), *i.e.* are "generally recognized" by experts familiar with OTC medicines to be safe and effective for their intended uses, and thus not subject to the requirement of premarketing approval by an NDA under section 505(a) of the Act, 21 U.S.C. § 355(a). (App. 5a). In designing the Review, the FDA divided OTC ingredients into seventeen broad therapeutic categories, such as antacids, laxatives, internal analgesics, and dentifrices. The FDA then assigned each category to an outside advisory review panel chosen by the agency from among academicians, practicing physicians and pharmacists, and research scientists.

The advisory panels were asked to review all data on the safety and effectiveness of OTC drugs and the labeling on such marketed products, and to issue proposed reports (or "monographs") to the FDA Commissioner with recommendations regarding the ingredients, dosage levels, permissible combinations, warnings, and other precautions which should be allowed or required of OTC medicines in various product categories. The FDA proposes that OTC drugs must conform to each of the specific conditions contained in final monographs

as well as to general conditions established by the OTC Drug Review. *See* 21 C.F.R. § 330.1(a)-(j) (1981). (App. 2b-3b).

The OTC Drug Review thus allows the FDA to determine which OTC drugs are generally recognized by experts as safe and effective and not misbranded under recommended or suggested conditions of use. Once review of a particular category is completed, the FDA determines whether an OTC drug can meet the conditions established, or whether the drug is subject to an approved NDA prior to marketing.[6] Proposed monographs have been published with respect to all of the major therapeutic classes of OTC drugs. *See* 46 Fed. Reg. 47,730 (1981).

This ongoing proceeding is a highly complicated undertaking by the FDA, one reflecting a complex approach toward substantive scientific determinations that have been the focus of more than ten years of extensive government and industry discussion and effort. Considerable additional effort remains before this massive program is to be concluded.

SUMMARY OF ARGUMENT

The issue squarely presented to this Court is whether certain generic prescription drug products distributed by respondents are exempt from the requirement of premarketing clearance by the FDA. At no stage below was the issue of over-the-counter drugs or their regulation by the FDA under the OTC Drug Review addressed in the courts' decisions or made a part of the evidentiary record. Nevertheless, the legality of the OTC Drug Review is now inappropriately and belatedly being questioned by respondents. The opinions of the courts below

[6] The OTC Drug Review similarly facilitates a determination as to whether a drug is "grandfathered," or is to be found to be misbranded due to a change in its formulation and/or labeling. Section 201(p) of the Act, 21 U.S.C. § 321(p), "grandfathers" pre-1938 drugs, the labeling of which still contains the same representations concerning their use, and section 107(c)(4) of the 1962 Drug Amendments, Pub. L. No. 87-781, 21 U.S.C. § 321 *note*, "grandfathers" pre-1962 drugs, which were generally recognized as safe and not covered by an effective NDA in 1962 and the labeling of which still contains the same representations concerning their use.

never examined the issue of OTC drugs and thus respondents' question, were it to be considered, would be under judicial consideration for the first time in this case by this Court.

It is respectfully submitted that a proper judicial assessment regarding the legality of the OTC Drug Review would necessarily require development of an adequate record to consider, for example, such matters as expert testimony on safety and effectiveness issues pertaining to OTC drugs, pertinent legislative history of the Act, the exercise of appropriate administrative discretion by the FDA in carrying out its statutory mandate, and the historic recognition of the fundamental legal and scientific distinctions between prescription and OTC drugs.

Under these circumstances, *amicus* submits that the legality of the OTC Drug Review and current regulation of OTC drugs by the FDA are not properly at issue here and should not be the subject of judicial consideration in this case.

ARGUMENT

OVER-THE-COUNTER DRUGS AND THE LEGALITY OF THEIR REGULATION BY THE FDA UNDER THE OTC DRUG REVIEW ARE NOT PROPERLY AT ISSUE IN THIS CASE.

I. The District Court And The Court Of Appeals Decisions Below Never Addressed OTC Drugs Or Their Regulation By The FDA And Therefore Such Issues Would Be Questions Of First Impression Before This Court.

Neither the district court nor the Court of Appeals for the Eleventh Circuit, in their respective decisions, referenced or discussed over-the-counter drugs or their regulation by the FDA. The district court record was developed at a preliminary injunction hearing and the expert witnesses who appeared presented evidence concerning the safety and effectiveness of generic prescription drugs. None testified regarding OTC drugs or the OTC Drug Review, and the district court's opinion did not address such matters. Similarly, on appeal the Eleventh Circuit expressed no opinion on the FDA's regulation of OTC

drugs; the matter was neither at issue below nor necessary to consider in order to reach its holding.[7]

If this Court were to address OTC drugs and their regulation by the FDA, it would constitute the first time in this proceeding that such issues would be entertained.[8] The Government, under the strictures of Rule 21.1(a) of the Rules of this Court, has rightly presented the question in its petition for certiorari as concerning prescription drugs only. Rule 21.1(a) provides that the questions presented for review be "expressed in the terms and circumstances of the case" and that "[o]nly the questions set forth in the petition or fairly included therein will be considered by the Court." As petitioner, the Government may not raise issues in its brief on the merits which were not raised properly in the petition for certiorari, *F.D. Rich Co.* v. *Industrial Lumber Co.*, 417 U.S. 116, 121 n.6 (1974), and, furthermore, the Government is not entitled to a decision on any questions other than those formally presented by its petition. *General Talking Pictures Corp.* v. *Western Electric Co.*, 304 U.S. 175, 177-79 (1938).

Similarly, where an issue is first brought to the Court's attention in a reply brief to a petition, as here, it is not deemed properly before the Court. *Namet* v. *United States*, 373 U.S. 179, 190 & n.11 (1963). Though respondents as the prevailing party may suggest different questions in an effort to support the

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[7] Even though Generix, as appellant, sought to raise doubts about the FDA's position by briefly noting the agency's approach toward OTC drugs (Brief for Appellants at 26-28), the Court of Appeals did not consider that point in its opinion in reaching a decision favorable to Generix. In response, the Government, as appellee, insisted that FDA's classification of OTC drugs under the OTC Drug Review was not at issue in the case. (Brief For Appellee United States of America at 25 n.20). Generix in its reply did not challenge this assertion by the Government.

[8] It should be noted that in a prior opinion of the Court, there was brief consideration of the OTC Drug Review. In *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645 (1973), the Court took note of the apparent impossibility of reviewing hundreds of thousands of OTC drugs on a case-by-case basis under the standards of the 1962 Drug Amendments. The prospect of individual *de novo* proceedings for each and every OTC drug product, by agency adjudication or separate seizure actions, argued for the approach adopted in the OTC Drug Review as a means to accomplish the agency's broad responsibilities under the Act. *Id.* at 650.

judgment below, those issues must appear in the record in order to provide a factual basis for the Court to address such questions properly. *Cf. United States* v. *New York Telephone Co.*, 434 U.S. 159, 166 n.8 (1977) (issues raised by respondent were considered by lower courts and fully argued); *Dandridge* v. *Williams*, 397 U.S. 471, 475-76 n.6 (1970) (same). Based upon these principles, *amicus* submits that OTC drugs and the OTC Drug Review would involve issues of first impression before this Court, a consequence which would contravene sound judicial practice and principles of fundamental fairness.[9]

II. An Adequate Record Is A Prerequisite To Consideration Of Issues Governing FDA Regulation Of OTC Drugs.

No appropriate consideration by this Court of the legal issues peculiar to federal regulation of the manufacture and sale of OTC drugs can be obtained in the absence of an adequate record on the subject. Such a record would, among other things, include the historic recognition by the Congress, the courts, and the FDA of the important differences between prescription and OTC drugs and the dissimilar scientific determinations made with respect to these two classes of drugs. Moreover, as noted previously, there is no record below that bears upon either the safety or effectiveness of OTC drugs or the procedures and assumptions used with respect to the OTC Drug Review.

One determination relevant to the legality of present OTC drug regulation would be scientific and medical testimony by experts regarding the analysis applied in determining general recognition of the safety and effectiveness of OTC drugs as distinct from prescription drugs. As section 201(p) of the Act, 21 U.S.C. § 321(p), provides, a drug is not deemed a "new drug" if it receives "general recognition" by experts qualified by scientific training and experience to make safety and effectiveness evaluations. Yet, none of the experts testifying below examined issues of "general recognition" with regard to OTC drugs.

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[9] Had OTC drug regulation been at issue in the district court proceeding, OTC drug manufacturers and/or *amicus* would have been entitled to reasonable notice and an opportunity to be heard on the merits in order to protect their rights. *See generally Mullane* v. *Central Hanover Trust Co.*, 339 U.S. 306, 313-15 (1950).

With reference to the specific dispute between the parties in this proceeding, neither the courts below nor this Court have available any evidence, for example, relating to bioavailability or bioequivalency as those factors might affect the "general recognition" of the safe and effective use of OTC drugs.

The Act and its legislative history read as a whole acknowledge the substantive differences between prescription drugs and OTC medicines. These differences essentially relate to the conditions under which and for which the two classifications of drugs are used. Over-the-counter drugs are designed to treat symptoms of minor ailments that are easily recognized by consumers and are self-limiting in duration. Unlike OTCs, prescription drugs are generally used for serious or life-threatening conditions, such as high blood pressure.[10]

Recognition of this important distinction between prescription and OTC drugs is reflected not only in the Act,[11] but

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[10] FDA's initiation of this particular lawsuit against Generix was apparently prompted by agency concern over potential safety and effectiveness problems with generic prescription drugs prescribed to treat such serious conditions as hyper-aldosteronism, hypertension, and edema. 498 F. Supp. at 289-90.

[11] For example, in adopting the Durham-Humphrey Amendments of 1951, Pub. L. No. 82-215 § 1, 65 Stat. 648, which amended the Act to deal more directly with the labeling and dispensing of drugs that may be sold only by prescription, Congress considered the differences between the two general classifications of drugs. *See* S. REP. NO. 946, 82d Cong., 1st Sess. 3, *reprinted in*, 1951 U.S. CODE CONG. & ADM. NEWS 2424, 2456; H. REP. NO. 700, 82d Cong., 1st Sess. 3-4 (1951). There was extensive debate in committee and on the floor over whether the newly created "prescription drug" category (today codified at 21 U.S.C. § 353(b)(1)) (App. 4a-5a) was going to be used to place obviously safe OTC drugs onto a prescription drug list and restrict their availability for self-medication. *See United States* v. *Article of Drug . . . . Decholin*, 264 F. Supp. 473, 478-84 (E.D. Mich. 1967). Indeed, the distinction between prescription and OTC drugs was repeatedly noted during subcommittee hearings. *Durham-Humphrey Amendments of 1951: Hearings on S.1552 Before the Kefauver Subcomm. of the Senate Comm. on Labor and Public Welfare*, 82d Cong., 1st Sess. (1951) (Transcript at 2, 6, 28, 35, 298).

In connection with passage of the 1962 Drug Amendments, Pub. L. No. 87-781, §§ 112(a), 131(a), 76 Stat. 780, 790, 791, Congress again recognized

(*footnote continues*)

also by the lower courts[12] and the FDA.[13] It is for sound reasons that there exist these two classifications of drugs, meriting dissimilar regulatory approaches that might be adopted by the FDA.

This brief does not, of course, purport to provide a comprehensive review of the Act and its legislative history, or the repeated and pervasive judicial, administrative, and scientific recognition of the prescription/OTC distinction. Yet such

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(*footnote continued*)

the differences between prescription and OTC drugs by establishing under its misbranding provisions separate advertising and labeling requirements for prescription drugs only. It should be noted that regulation of the advertising of OTC drugs is not even subject to the jurisdiction of the FDA, but instead is governed by an entirely separate agency, the Federal Trade Commision. Thus, as codified at section 502(n) of the Act, 21 U.S.C. § 352(n), prescription-drug advertising is required to show the established name of the particular drug, the quantitative formula as used in its labeling, a brief summary of adverse side effects, contraindications, efficacy, and other information for the guidance of physicians. (App. 3a-4a). Similarly, section 502(e) of the Act, 21 U.S.C. § 352(e), sets forth certain specific labeling requirements for stating the quantity of active ingredients in the drug product, which are applicable only to prescription drugs. (App. 1a-3a).

[12] For example, in *United States* v. *Articles of Drug . . . Hormonin*, 498 F. Supp. 424, 432 (D. N.J. 1980), *aff'd*, No. 81-1035 (3d Cir., Sept. 15, 1981), a district court made the following observation concerning the FDA's regulation of OTC drugs:

> [W]ith respect to OTC drugs, approval [under the OTC Drug Review] is contingent upon "controlled clinical investigations . . . unless . . . waived on . . . a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and . . . an alternative method of investigation is adequate to substantiate effectiveness." 21 C.F.R. § 330.10(a)(4)(ii). Thus, an OTC drug presumptively requires clinical investigation of effectiveness. Even if such requirements had been eliminated, . . . such a reduced standard could be rationally based upon the decreased risk to public health presented by OTC drugs.

[13] Within the FDA itself, separate regulations have been adopted to govern prescription and OTC drugs as distinct classifications, consistent with the agency's scientific assessments as to the relative risks to the public. *Compare* 21 C.F.R. §§ 310.200-.201; Part 361 (prescription drugs) *with* 21 C.F.R. Parts 330, 331 & 332 (OTC drugs).

matters would have to be developed in a record by the lower courts in order for this Court to have the information to resolve the issues concerning OTC drugs, which respondents have now tried to interject—unnecessarily—into this case. This proceeding can and should focus on the question properly presented to the Court for review, namely, the applicability of the "new drug" provisions of the Act as they relate to the sale of generic prescription drug products. Issues relating to OTC drugs and their regulation by the FDA have not been remotely explored below and should not be addressed in this proceeding.

CONCLUSION

The Proprietary Association respectfully submits that OTC drugs and their regulation by the FDA are not properly at issue in this case.

Respectfully submitted,

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April 15, 1982

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APPENDIX A

21 U.S.C. § 321 provides in pertinent part:

For the purposes of this chapter—

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to June 25, 1938, it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

* * *

21 U.S.C. § 352 provides in pertinent part:

A drug or device shall be deemed to be misbranded—

* * *

(e)(1) If it is a drug, unless (A) its label bears, to the exclusion of any other nonproprietary name (except the applicable systematic chemical name or the chemical formula), (i) the established name (as defined in paragraph (3)) of the drug, if such there be, and (ii), in case it is

fabricated from two or more ingredients, the established name and quantity of each active ingredient, including the quantity, kind, and proportion of any alcohol, and also including, whether active or not, the established name and quantity or proportion of any bromides, ether, chloroform, acetanilid, acetphenetidin, amidopyrine, antipyrine, atropine, hyoscine, hyoscyamine, arsenic, digitalis, digitalis glucosides, mercury ouabain strophanthin, strychnine, thyroid, or any derivative or preparation of any such substances, contained therein: *Provided,* That the requirement for stating the quantity of the active ingredients, other than the quantity of those specifically named in this subsection, shall apply only to prescription drugs; and (B) for any prescription drug the established name of such drug or ingredient, as the case may be, on such label (and on any labeling on which a name for such drug or ingredient is used) is printed prominently and in type at least half as large as that used thereon for any proprietary name or designation for such drug or ingredient: *Provided,* That to the extent that compliance with the requirements of clause (A)(ii) or clause (B) of this paragraph is impracticable, exemptions shall be established by regulations promulgated by the Secretary.

(2) If it is a device and it has an established name, unless its label bears, to the exclusion of any other nonproprietary name, its established name (as defined in paragraph (4)) prominently printed in type at least half as large as that used thereon for any proprietary name or designation for such device, except that to the extent compliance with the requirements of this paragraph is impracticable, exemptions shall be established by regulations promulgated by the Secretary.

(3) As used in paragraph (1), the term "established name", with respect to a drug or ingredient thereof, means (A) the applicable official name designated pursuant to section 358 of this title, or (B), if there is no such name and such drug, or such ingredient, is an article recognized in an official compendium, then the official title thereof in

such compendium, or (C) if neither clause (A) nor clause (B) of this paragraph applies, then the common or usual name, if any, of such drug or of such ingredient: *Provided further,* That where clause (B) of this paragraph applies to an article recognized in the United States Pharmacopeia and in the Homeopathic Pharmacopoeia under different official titles, the official title used in the United States Pharmacopeia shall apply unless it is labeled and offered for sale as a homeopathic drug, in which case the official title used in the Homeopathic Pharmacopoeia shall apply.

(4) As used in paragraph (2), the term "established name" with respect to a device means (A) the applicable official name of the device designated pursuant to section 358 of this title, (B) if there is no such name and such device is an article recognized in an official compendium, then the official title thereof in such compendium, or (C) if neither clause (A) nor clause (B) of this paragraph applies, then any common or usual name of such device.

* * *

(n) In the case of any prescription drug distributed or offered for sale in any State, unless the manufacturer, packer, or distributor thereof includes in all advertisements and other descriptive printed matter issued or caused to be issued by the manufacturer, packer, or distributor with respect to that drug a true statement of (1) the established name as defined in subsection (e) of this section, printed prominently and in type at least half as large as that used for any trade or brand name thereof, (2) the formula showing quantitatively each ingredient of such drug to the extent required for labels under subsection (e) of this section, and (3) such other information in brief summary relating to side effects, contraindications, and effectiveness as shall be required in regulations which shall be issued by the Secretary in accordance with the procedure specified in section 371(e) of this title: *Provided,* That (A) except in extraordinary circumstances, no regulation issued under

this subsection shall require prior approval by the Secretary of the content of any advertisement, and (B) no advertisement of a prescription drug, published after the effective date of regulations issued under this subsection applicable to advertisements of prescription drugs, shall, with respect to the matters specified in this subsection or covered by such regulations, be subject to the provisions of sections 52 to 57 of Title 15. This subsection (n) shall not be applicable to any printed matter which the Secretary determines to be labeling as defined in section 321(m) of this title. Nothing in the Convention on Psychotropic Substances, signed at Vienna, Austria, on February 21, 1971, shall be construed to prevent drug price communications to consumers.

* * *

21 U.S.C. § *353* provides in pertinent part:

* * *

(b)(1) A drug intended for use by man which—

(A) is a habit-forming drug to which section 352(d) of this title applies; or

(B) because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug; or

(C) is limited by an approved application under section 355 of this title to use under the professional supervision of a practitioner licensed by law to administer such drug,

shall be dispensed only (i) upon a written prescription of a practitioner licensed by law to administer such drug, or (ii) upon an oral prescription of such practitioner which is reduced promptly to writing and filed by the pharmacist, or (iii) by refilling any such written or oral prescription if such refilling is authorized by the prescriber either in the original prescription or by oral order which is reduced

promptly to writing and filed by the pharmacist. The act of dispensing a drug contrary to the provisions of this paragraph shall be deemed to be an act which results in the drug being misbranded while held for sale.

* * *

21 U.S.C. § 355 provides in pertinent part:

(a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) of this section is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug.

* * *

APPENDIX B

PART 330—OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED

Subpart A—General Provisions

Sec.

330.1 General conditions for general recognition as safe, effective and not misbranded.

330.5 Drug categories.

Subpart B—Administrative Procedures

330.10 Procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded, and for establishing monographs.

330.11 NDA deviations from applicable monograph.

330.12 Status of over-the-counter (OTC) drugs previously reviewed under the Drug Efficacy Study (DESI).

330.13 Conditions for marketing ingredients recommended for over-the-counter (OTC) use under the OTC drug review.

AUTHORITY: Secs. 502, 503, 505, 601, 52 Stat. 1051, 1052, 1053, 1055, as amended (21 U.S.C. 352, 353, 355, 371) (5 U.S.C. 554), unless otherwise noted.

Subpart A—General Provisions

§ *330.1 General conditions for general recognition as safe, effective and not misbranded.*

An over-the-counter (OTC) drug listed in this subchapter is generally recognized as safe and effective and is not misbranded if it meets each of the conditions contained in this part and each of the conditions contained in any applicable monograph. Any product which fails to conform to each of the conditions contained in this part and in an applicable monograph is liable to regulatory action.

(a) The product is manufactured in compliance with current good manufacturing practices, as established by Parts 210, 211, 225, 226 and 229 of this chapter.

(b) The establishment(s) in which the drug product is manufactured is registered, and the drug product is listed, in compliance with Part 207 of this chapter. It is requested but not required that the number assigned to the product pursuant to Part 207 of this chapter appear on all drug labels and in all drug labeling. If this number is used, it shall be placed in the manner set forth in Part 207 of this chapter.

(c) The product is labeled in compliance with Chapter V of the act and Subchapter C et seq. of this chapter. For purposes of § 201.61(b) of this chapter, the statement of identity of the product shall be the term or phrase used in the applicable monograph established in this part.

(d) The advertising for the product prescribes, recommends, or suggests its use only under the conditions stated in the labeling.

(e) The product contains only suitable inactive ingredients which are safe in the amounts administered and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity. Color additives may be used only in accordance with section 706 of the act and Subchapter A of this chapter.

(f) The product container and container components meet the requirements of § 211.22 of this chapter.

(g) The labeling for all drugs contains the general warning: "Keep this and all drugs out of the reach of children." The labeling of drugs used for oral administration shall also state: "In case of accidental overdose, seek professional assistance or contact a poison control center immediately." The labeling for drugs administered rectally or used topically shall state: "In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately." The Food and Drug Admin-

istration will grant an exemption from these general warnings where appropriate upon petition, which shall be maintained in a permanent file for public review by the Dockets Management Branch, Food and Drug Administration, Room 4-62, Parklawn Building, 5600 Fishers Lane, Rockville, MD 20857.

(h) Where no maximum daily dosage limit for an active ingredient is established in this part, it is used in a product at a level that does not exceed the amount reasonably required to achieve its intended effect.

(i) [Reserved]

(j) It is recommended that the labeling of the product contain the quantitative amount of each active ingredient, expressed in terms of the dosage unit stated in the directions for use (e.g., tablet, teaspoonful).

§ *330.5 Drug categories.*

Monographs promulgated pursuant to the provisions of this part shall be established in this Part 330 and following parts and shall cover the following designated categories:

(a) Antacids.

(b) Laxatives.

(c) Antidiarrheal products.

(d) Emetics.

(e) Antiemetics.

(f) Antiperspirants.

(g) Sunburn prevention and treatment products.

(h) Vitamin-mineral products.

(i) Antimicrobial products.

(j) Dandruff products.

(k) Oral hygiene aids.

(l) Hemorrhoidal products.

(m) Hematinics.

(n) Bronchodilator and antiasthmatic products.

(o) Analgesics.

(p) Sedatives and sleep aids.

(q) Stimulants.

(r) Antitussives.

(s) Allergy treatment products.

(t) Cold remedies.

(u) Antirheumatic products.

(v) Ophthalmic products.

(w) Contraceptive products.

(x) Miscellaneous dermatologic products.

(y) Dentifrices and dental products such as analgesics, antiseptics, etc.

(z) Miscellaneous (all other OTC drugs not falling within one of the above therapeutic categories).

Subpart B—Administrative Procedures

§ *330.10 Procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded, and for establishing monographs.*

For purposes of classifying over-the-counter (OTC) drugs as drugs generally recognized among qualified experts as safe and effective for use and as not misbranded drugs, the following regulations shall apply:

(a) *Procedure for establishing OTC drug monographs*—(1) *Advisory review panels.* The Commissioner shall appoint advisory review panels of qualified experts to evaluate the safety and effectiveness of OTC drugs, to review OTC drug labeling, and to advise him on the promulgation of monographs establishing conditions under which OTC drugs are generally recognized as safe and

effective and not misbranded. A single advisory review panel shall be established for each designated category of OTC drugs and every OTC drug category will be considered by a panel. The members of a panel shall be qualified experts (appointed by the Commissioner) and may include persons from lists submitted by organizations representing professional, consumer, and industry interests. The Commissioner shall designate the chairman of each panel. Summary minutes of all meetings shall be made.

(2) *Request for data and views.* The Commissioner will publish a notice in the FEDERAL REGISTER requesting interested persons to submit, for review and evaluation by an advisory review panel, published and unpublished data and information pertinent to a designated category of OTC drugs. Data and information submitted pursuant to a published notice, and falling within the confidentiality provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j), shall be handled by the advisory review panel and the Food and Drug Administration as confidential until publication of a proposed monograph and the full report(s) of the panel. Thirty days thereafter such data and information shall be made publicly available and may be viewed at the office of the Dockets Management Branch of the Food and Drug Administration, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of one or more of those statutes. To be considered, eight copies of the data and/or views on any marketed drug within the class must be submitted, preferably bound, indexed, and on standard sized paper (approximately 8 1/2 x 11 inches). When requested, abbreviated submissions should be sent. All submissions must be in the following format:

OTC DRUG REVIEW INFORMATION

I. Label(s) and all labeling (preferably mounted and filed with the other data—facsimile labeling is acceptable in lieu of actual container labeling).

II. A statement setting forth the quantities of active ingredients of the drug.

III. Animal safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

IV. Human safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of the finished drug product.

5. Pertinent medical and scientific literature.

V. Efficacy data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of the finished drug product.

5. Pertinent medical and scientific literature.

VI. A summary of the data and views setting forth the medical rationale and purpose (or lack thereof) for the drug and its ingredients and the scientific basis (or lack thereof) for the conclusion that the drug and its ingredients have been proven safe and effective for the intended use. If there is an absence of controlled studies in the material submitted, an explanation as to why such studies are not considered necessary must be included.

(3) *Deliberations of an advisory review panel.* An advisory review panel will meet as often and for as long as is appropriate to review the data submitted to it and to prepare a report containing its conclusions and recommendations to the Commissioner with respect to the safety and effectiveness of the drugs in a designated category of OTC drugs. A panel may consult any individual or group. Any interested person may request an opportunity to present oral views to the panel; such request may be granted or denied by the panel. Such requests for oral presentations should be in written form including a summarization of the data to be presented to the panel. Any interested person may present written data and views which shall be considered by the panel. This information shall be presented to the panel in the format set forth in paragraph (a)(2) of this section and within the time period established for the drug category in the notice for review by a panel.

(4) *Standards for safety, effectiveness, and labeling.* The advisory review panel, in reviewing the data submitted to it and preparing its conclusions and recommendations, and the Commissioner, in reviewing the conclusions and recommendations of the panel and the published proposed, tentative, and the final monographs, shall apply the following standards to determine general recognition that a category of OTC drugs is safe and effective and not misbranded:

(i) Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

(ii) Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed. Proof of effectiveness shall consist of controlled clinical investigations as defined in § 314.111(a)(5)(ii) of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered. General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

(iii) The benefit-to-risk ratio of a drug shall be considered in determining safety and effectiveness.

(iv) An OTC drug may combine two or more safe and effective active ingredients and may be

generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

(v) Labeling shall be clear and truthful in all respects and may not be false or misleading in any particular. It shall state the intended uses and results of the product; adequate directions for proper use; and warnings against unsafe use, side effects, and adverse reactions in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use.

(vi) A drug shall be permitted for OTC sale and use by the laity unless, because of its toxicity or other potential for harmful effect or because of the method or collateral measures necessary to its use, it may safely be sold and used only under the supervision of a practitioner licensed by law to administer such drugs.

(5) *Advisory review panel report to the Commissioner.* An advisory review panel shall submit to the Commissioner a report containing its conclusions and recommendations with respect to the conditions under which OTC drugs falling within the category covered by the panel are generally recognized as safe and effective and not misbranded. Included within this report shall be:

(i) A recommended monograph or monographs covering the category of OTC drugs and establishing conditions under which the drugs involved are generally recognized as safe and effective and not misbranded (Category I). This monograph may include any conditions relating to active ingredients, labeling

indications, warnings and adequate directions for use, prescription or OTC status, and any other conditions necessary and appropriate for the safety and effectiveness of drugs covered by the monograph.

(ii) A statement of all active ingredients, labeling claims or other statements, or other conditions reviewed and excluded from the monograph on the basis of the panel's determination that they would result in the drug's not being generally recognized as safe and effective or would result in misbranding (Category II).

(iii) A statement of all active ingredients, labeling claims or other statements, or other conditions reviewed and excluded from the monograph on the basis of the panel's determination that the available data are insufficient to classify such condition under either paragraph (a)(5)(i) or (ii) of this section and for which further testing is therefore required (Category III). The report may recommend the type of further testing required and the time period within which it might reasonably be concluded.

(6) *Proposed monograph.* After reviewing the conclusions and recommendations of the advisory review panel, the Commissioner shall publish in the FEDERAL REGISTER a proposed order containing:

(i) A monograph or monographs establishing conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded (Category I).

(ii) A statement of the conditions excluded from the monograph on the basis of the Commissioner's determination that they would result in the drug's not being generally recognized as safe and effective or would result in misbranding (Category II).

(iii) A statement of the conditions excluded from the monograph on the basis of the Commissioner's determination that the available data are insufficient

to classify such conditions under either paragraph (a)(6)(i) or (ii) of this section (Category III).

(iv) The full report(s) of the panel to the Commissioner.

The proposed order shall specify a reasonable period of time within which conditions falling within paragraph (a)(6)(iii) of this section may be continued in marketed products while the data necessary to support them are being obtained for evaluation by the Food and Drug Administration. The summary minutes of the panel meetings shall be made available to interested persons upon request. Any interested person may, within 90 days after publication of the proposed order in the FEDERAL REGISTER, file with the Dockets Management Branch of the Food and Drug Administration written comments in quintuplicate. Comments may be accompanied by a memorandum or brief in support thereof. All comments may be reviewed at the office of the Dockets Management Branch during regular working hours, Monday through Friday. Within 30 days after the final day for submission of comments, reply comments may be filed with the Dockets Management Branch; these comments shall be utilized to reply to comments made by other interested persons and not to reiterate a position. The Commissioner may satisfy this requirement by publishing in the FEDERAL REGISTER a proposed order summarizing the full report of the advisory review panel, containing its conclusions and recommendations, to obtain full public comment before undertaking his own evaluation and decision on the matters involved.

(7) *Tentative final monograph.* (i) After reviewing all comments, reply comments, and any new data and information, the Commissioner shall publish in the FEDERAL REGISTER a tentative order containing a monograph establishing conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded. Within 60 days, any interested person may file with the Dockets Management Branch, Food and Drug Administration, written comments or written objections specifying with particularity the omissions or additions

requested. These objections are to be supported by a brief statement of the grounds therefor. A request for an oral hearing may accompany such objections.

(ii) The Commissioner may publish in the FEDERAL REGISTER a separate tentative order containing a statement of those active ingredients reviewed and proposed to be excluded from the monograph on the basis of the Commissioner's determination that they would result in a drug product not being generally recognized as safe and effective or would result in misbranding, and for which no substantive comments in opposition to the panel report or new data and information were received by the Food and Drug Administration pursuant to paragraph (a)(6)(iv) of this section. Within 60 days, any interested person may file with the Dockets Management Branch, Food and Drug Administration, written objections specifying with particularity the provision of the tentative order to which objection is made. These objections are to be supported by a brief statement of the grounds therefor. A request for an oral hearing may accompany such objections.

(iii) Within 12 months after publishing a tentative order pursuant to paragraph (a)(7)(i) of this section, any interested person may file with the Dockets Management Branch, Food and Drug Administration, new data and information to support a condition excluded from the monograph in the tentative order.

(iv) Within 60 days after the final day for submission of new data and information, comments on the new data and information may be filed with the Dockets Management Branch, Food and Drug Administration.

(v) New data and information submitted after the time specified in this paragraph but prior to the establishment of a final monograph will be considered as a petition to amend the monograph and will be considered by the Commissioner only after a final

monograph has been published in the FEDERAL REGISTER unless the Commissioner finds that good cause has been shown that warrants earlier consideration.

(8) *Oral hearing before the Commissioner.* After reviewing objections filed in response to the tentative final monograph, the Commissioner, if he finds reasonable grounds in support thereof, shall by notice in the FEDERAL REGISTER schedule an oral hearing. The notice scheduling an oral hearing shall specify the length of the hearing and how the time shall be divided among the parties requesting the hearing. The hearing shall be conducted by the Commissioner and may not be delegated.

(9) *Final monograph.* After reviewing the objections, the entire administrative record including all new data and information and comments, and considering the arguments made at any oral hearing, the Commissioner shall publish in the FEDERAL REGISTER a final order containing a monograph establishing conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded. The monograph shall become effective as specified in the order.

(10) *Administrative record.* (i) All data and information to be considered in any proceeding pursuant to this section shall be submitted in response to the request for data and views pursuant to paragraph (a)(2) of this section or accepted by the panel during its deliberations pursuant to paragraph (a)(3) of this section or submitted to the Dockets Management Branch as part of the comments during the 90-day period and 30-day rebuttal comment period permitted pursuant to paragraph (a)(6) of this section or submitted to the Dockets Management Branch during the 12-month period or as part of the comments during the 60-day period permitted pursuant to paragraph (a)(7) of this section.

(ii) The Commissioner shall make all decisions and issue all orders pursuant to this section solely on

the basis of the administrative record, and shall not consider data or information not included as part of the administrative record.

(iii) The administrative record shall consist solely of the following material: All notices and orders published in the FEDERAL REGISTER, all data and views submitted in response to the request published pursuant to paragraph (a)(2) of this section or accepted by the panel during its deliberations pursuant to paragraph (a)(3) of this section, all minutes of panel meetings, the panel report(s), all comments and rebuttal comments submitted on the proposed monograph and all new data and information submitted pursuant to paragraph (a)(6) of this section, all objections submitted on the tentative final monograph and all new data and information and comments submitted pursuant to paragraph (a)(7) of this section, the complete record of any oral public hearing conducted pursuant to paragraph (a)(8) of this section, all other comments requested at any time by the Commissioner, all data and information for which the Commissioner has reopened the administrative record, and all other material that the Commissioner includes in the administrative record as part of the basis for the Commissioner's decision.

(11) *Court appeal.* The monograph contained in the final order constitutes final agency action from which appeal lies to the courts. The Food and Drug Administration will request consolidation of all appeals in a single court. Upon court appeal, the Commissioner may, at his discretion, stay the effective date for part or all of the monograph pending appeal and final court adjudication.

(12) *Amendment of monographs.* (i) The Commissioner may propose on the Commissioner's own initiative to amend or repeal any monograph established pursuant to this section. Any interested person may petition the Commissioner for such proposal pursuant to § 10.30 of this chapter. The Commissioner may deny the petition if the Commissioner finds a lack of safety or effectiveness em-

ploying the standards in paragraph (a)(4) of this section (in which case the appeal provisions of paragraph (a)(11) of this section shall apply), or the Commissioner may publish a proposed amendment or repeal in the FEDERAL REGISTER if the Commissioner finds general recognition of safety and effectiveness employing the standards in paragraph (a)(4) of this section. Any interested person may, within 60 days after publication of the proposed order in the FEDERAL REGISTER, file with the Dockets Management Branch, Food and Drug Administration, written comments in quadruplicate. Comments may be accompanied by a memorandum or brief in support thereof. All comments may be reviewed in the Dockets Management Branch between the hours of 9 a.m. and 4 p.m., Monday through Friday. After reviewing the comments, the Commissioner shall publish a final order amending the monograph established under the provisions of paragraph (a)(9) of this section or withdraw the proposal if comments opposing the amendment are persuasive. A new drug application may be submitted in lieu of, or in addition to, a petition under this paragraph.

(ii) A new drug application may be submitted in lieu of a petition to amend the OTC drug monograph only if the drug product with the condition that is the subject of the new drug application has not been marketed on an interim basis (such as under the provisions of paragraph (a)(6)(iii) of this section), all clinical testing has been conducted pursuant to a new drug application plan, and no marketing of the product with the condition for which approval is sought is undertaken prior to approval of the new drug application. The Food and Drug Administration shall handle a new drug application as a petition for amendment of a monograph, and shall review it on that basis, if the provisions of this paragraph preclude approval of a new drug application but permit the granting of such a petition.

(b) *Regulatory action.* Any product which fails to conform to an applicable monograph after its effective date is liable to regulatory action.

(c) Information and data submitted under this section shall include, with respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

(d) [Reserved]

(e) *Institutional review and informed consent.* Information and data submitted under this section after July 27, 1981, shall include statements regarding each clinical investigation involving human subjects, from which the information and data are derived, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, areas not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

§ *330.11 NDA from applicable monograph.*

A new drug application requesting approval of an OTC drug deviating in any respect from a monograph that has become final shall be in the form required by § 314.1(a)(2) of this chapter, but shall include a statement that the product meets all conditions of the applicable monograph except for the deviation for which approval is requested and may omit all information except that pertinent to the deviation.

§ *330.12 Status of over-the-counter (OTC) drugs previously reviewed under the Drug Efficacy Study (DESI).*

(a) There were 420 OTC drugs reviewed in the Drug Efficacy Study (a review of drugs introduced to the market through new drug procedures between 1938 and 1962). A careful review has been made of the reports on these drugs to determine those drugs for which implementation may be

deferred without significant risk to the public health, pending review by appropriate OTC drug advisory review panels and promulgation of a monograph.

(b) On and after April 20, 1972, a number of notices were published in the FEDERAL REGISTER concerning previously unpublished OTC drugs reviewed by the National Academy of Sciences-National Research Council Drug Efficacy Study Group. Only the evaluations and comments of the panels were published, with no conclusions of the Commissioner of Food and Drugs. Those publications were for the purpose of giving interested persons the benefit of the Academy's opinions. For those products, and also for OTC drug products previously published with the Commissioner's conclusions (except for the products listed in paragraph (b)(1) and (2) of this section), all requests for data, revised labeling, requests for new drug applications, abbreviated new drug applications, updating supplements, data to support less than effective claims, if any, etc., are deferred, and such OTC drug products are instead subject to the OTC drug review in their appropriate classes pursuant to the procedures established in this subpart.

(1) The requirements of the following DESI announcements are not deferred (the reference document may also pertain to prescription drugs):

(i) Certain Surgical Sutures (DESI 4725), published in the FEDERAL REGISTER of November 11, 1971 (36 FR 21612).

(ii) Absorbable Dusting Powder (DESI 6264), published in the FEDERAL REGISTER of May 25, 1971 (36 FR 9475).

(iii) Certain Insulin Preparations (DESI 4286), published in the FEDERAL REGISTER of April 9, 1971 (36 FR 6842).

(iv) Sulfo-Van Ointment (DESI 2230), published in the FEDERAL REGISTER of October 8, 1970 (35 FR 15860).

(v) Antiperspirants and Deodorants Containing Neomycin Sulfate (DESI 11048) for which an order revoking provisions for certification or release was published in the FEDERAL REGISTER of December 5, 1972 (37 FR 25820) and has been stayed by the filing of objections.

(vi) Thorexin Cough Medicine (DESI 11160) for which a notice of opportunity for hearing was published in the FEDERAL REGISTER of February 2, 1973 (38 FR 3210).

(vii) Antibiotic susceptibility discs (DESI 90235) for which an order providing for certain discs to be certified and removing provisions for certification of other discs was published in the FEDERAL REGISTER of September 30, 1972 (37 FR 20525) and has been stayed by the filing of objections notice of which was published in the FEDERAL REGISTER of March 15, 1973 (38 FR 7007).

(2) Deferral of requirements is not appropriate when an announcement has been published and has been followed by a final order classifying a drug either as lacking substantial evidence of effectiveness or as not shown to be safe. These products will be removed from the market, if they have not already been removed. Regulatory action will also be undertaken against identical, similar and related products (21 CFR 310.6). Deferral of requirements is not appropriate for the following (the referenced document may also pertain to prescription drugs):

(i) Certain Sulfonamide-Decongestant Nasal Preparation (DESI 4850), for which notice of withdrawal of approval of new drug applications was published in the FEDERAL REGISTER of October 24, 1970 (35 FR 16605, 16606).

(ii) Eskay's Theranates, containing strychnine, sodium, and calcium glycerophosphates, thiamine hydrochloride, alcohol, and phosphoric acid (DESI 2220), for which notice of withdrawal of approval of

the new drug application was published in the FEDERAL REGISTER of February 18, 1971 (36 FR 3152).

(iii) The following topical drugs (DESI 1726), for which notice of withdrawal of new drug applications was published in the FEDERAL REGISTER of August 28, 1971 (36 FR 17368):

(a) Rhulitol Solution, containing tannic acid, chlorobutanol, phenol, camphor, alum, and isopropyl alcohol.

(b) Zirnox Topical Lotion, containing phenyitoloxamine citrate and zirconium oxide.

(iv) Menacyl Tablets, containing aspirin, menadione, and ascorbic acid (DESI 6363), for which notice of withdrawal of approval of the new drug application was published in the FEDERAL REGISTER of July 23, 1970 (35 FR 11827).

(v) Curad Medicated Adhesive Bandage containing sulfathiazole (DESI 4964), for which notice of withdrawal of approval of the new drug application was published in the FEDERAL REGISTER of December 31, 1969 (34 FR 20441).

(vi) Drugs Containing Rutin, Quercetin, Hesperidin, or any Bioflavonoids (DESI 5960), for which notice of withdrawal of approval of new drug applications was published in the FEDERAL REGISTER of July 3, 1970 (35 FR 10872, 10873) and October 17, 1970 (35 FR 16332). A further notice of opportunity for hearing with respect to the drugs covered by the October 17, 1970 FEDERAL REGISTER notice will be published at a later date.

(vii) Antibiotics in Combination with Other Drugs for Nasal Use (DESI 7561), for which an order revoking provision for certification was published in the FEDERAL REGISTER of August 6, 1971 (36 FR 14469) and confirmed in the FEDERAL REGISTER of October 28, 1971 (36 FR 20686).

(viii) Antibiotic Troches (DESI 8328), for which an order revoking provision for certification was published in the FEDERAL REGISTER of July 14, 1971 (36 FR 13089) and confirmed in the FEDERAL REGISTER of October 9, 1971 (36 FR 19695).

(ix) Certain Drugs Containing Oxyphenisatin or Oxyphenisatin Acetate (DESI 10732), for which notices of withdrawal of approval of new drug applications were published in the FEDERAL REGISTER of February 1, 1972 (37 FR 2460), and March 9, 1973 (38 FR 6419).

(x) Curad Medicated Adhesive Bandage containing tyrothricin-nitrofurazone (DESI 5898), for which an order revoking provision for certification was published March 14, 1972 (37 FR 5294), and confirmed in the FEDERAL REGISTER of July 6, 1972 (37 FR 13254).

(xi) Candette Cough Gel (DESI 11562), for which notice of withdrawal of approval of the new drug application was published in the FEDERAL REGISTER of November 19, 1972 (37 FR 25249).

(xii) Certain OTC Multiple-Vitamin Preparations for Oral Use containing excessive amounts of vitamin D and/or vitamin A (DESI 97), for which notice of withdrawal of approval of the new drug applications was published in the FEDERAL REGISTER of November 29, 1972 (37 FR 25249).

(xiii) Certain Sulfonamide-Containing Preparations for Topical Ophthalmic or Otic Use (DESI 3684), for which a notice of withdrawal of approval was published in the FEDERAL REGISTER of February 2, 1973 (38 FR 3208).

(xiv) Those parts of the publication entitled "Certain Mouthwash and Gargle Preparations" (DESI 2855) pertaining to Tyrolaris Mouthwash, containing tyrothricin, panthenol, and alcohol, for

which an order revoking provision for certification was published in the FEDERAL REGISTER of February 2, 1967 (32 FR 1172) prior to the drug efficacy study implementation.

(c) Manufacturers and distributors should take notice that the information on OTC drugs provided by the Drug Efficacy Study review is valuable information as to the deficiencies in the data available to support indications for use. They are encouraged to perform studies to obtain adequate evidence of effectiveness for the review of OTC drugs which is already in progress. In the interim it is in the public interest that manufacturers and distributors of all OTC drugs effect changes in their formulations and/or labeling to bring the products into conformity with current medical knowledge and experience.

(d) Manufacturers and distributors of OTC drugs may be reluctant to make appropriate formulation and/or labeling changes for fear of losing the protection of the so-called "grandfather" provisions of the 1938 Federal Food, Drug, and Cosmetic Act (sec. 201(p)(1)) and the 1962 amendments to the act (sec. 107(c) of those amendments). To encourage and facilitate prompt changes, the Food and Drug Administration will not take legal action against any OTC drug, other than those not deferred, based on a charge that the product is a new drug and not grandfathered under the act as a result of the changes if the changes in formulation and/or labeling are of the following kind:

(1) The addition to the labeling of warning, contraindications, side effects, and/or precaution information.

(2) The deletion from the labeling of false, misleading, or unsupported indications for use or claims of effectiveness.

(3) Changes in the components or composition of the drug that will give increased assurance that the drug will have its intended effect, yet not raise or contribute any added safety questions.

(4) Changes in the components or composition of the drug which may reasonably be concluded to improve the safety of the drug, without diminishing its effectiveness.

(e) The forbearance from legal action for lack of grandfather protection is an interim procedure designed to encourage appropriate change in formulation and/or labeling during the time period required to review the various classes of OTC drugs. At such time as an applicable OTC drug monograph becomes effective, the interim procedure will automatically be terminated and any appropriate regulatory action will be initiated.

§ *330.13 Conditions for marketing ingredients recommended for over-the-counter (OTC) use under the OTC drug review*

(a) Before the publication in the FEDERAL REGISTER of an applicable proposed monograph, an OTC drug product that contains: (1) An active ingredient limited, on or after May 11, 1972, to prescription use for the indication and route of administration under consideration by an OTC advisory review panel, and not thereafter exempted from such limitation pursuant to § 310.200 of this chapter, or

(2) An active ingredient at a dosage level higher than that available in an OTC drug product on December 4, 1975, shall be regarded as a new drug within the meaning of section 201(p) of the act for which an approved new drug application is required.

(b)(1) An OTC drug product that contains: (i) An active ingredient limited, on or after May 11, 1972, to prescription use for the indication and route of administration under consideration by an OTC advisory review panel, and not thereafter exempted from such limitation pursuant to § 310.200 of this chapter, or

(ii) An active ingredient at a dosage level higher than that available in an OTC drug product on December 4, 1975, which ingredient and/or dosage

level is classified by the panel in category I (conditions subject to § 330.10(a)(6)(i)) shall be regarded as a new drug within the meaning of section 201(p) of the act for which an approved new drug application is required if marketed for OTC use prior to the date of publication in the FEDERAL REGISTER of a proposed monograph.

(2) An OTC drug product covered by paragraph (b)(1) of this section which is marketed after the date of publication in the FEDERAL REGISTER of a proposed monograph but prior to the effective date of a final monograph shall be subject to the risk that the Commissioner may not accept the panel's recommendation and may instead adopt a different position that may require relabeling, recall, or other regulatory action. The Commissioner may state such position at any time by notice in the FEDERAL REGISTER, either separately or as part of another document; appropriate regulatory action will commence immediately and will not await publication of a final monograph. Marketing of such a product with a formulation or labeling not in accord with a proposed monograph or tentative final monograph also may result in regulatory action against the product, the marketer, or both.

(c) An OTC drug product that contains: (1) An active ingredient limited, on or after May 11, 1972, to prescription use for the indication and route of administration under consideration by an OTC advisory review panel, and not thereafter exempted from such limitation pursuant to § 310.200 of this chapter, or

(2) An active ingredient at a dosage level higher than that available in any OTC drug product on December 4, 1975, which ingredient and/or dosage level is classified by the panel in category II (conditions subject to § 330.10(a)(6)(ii)), shall be regarded as a new drug within the meaning of section 201(p) of the act for which an approved new drug application is required for marketing.

(d) An OTC drug product that contains: (1) An active ingredient limited, on or after May 11, 1972, to prescription use for the indication and route of administration under consideration by an OTC advisory review panel, and not thereafter exempted from such limitation pursuant to § 310.200 of this chapter, or

(2) An active ingredient at a dosage level higher than that available in any OTC drug product on December 4, 1975 which ingredient and/or dosage level is classified by the panel in category III (conditions subject to § 330.10(a)(6)(iii)), may be lawfully marketed only after either the ingredient is determined by the Commissioner to be generally recognized as safe and effective, or a new drug application for the product has been approved.

Opposition

Office - Supreme Court, U.S.
FILED
[illegible] 1982
ALEXANDER L. STEVAS,
CLERK

No. 81-1222

in the Supreme Court of the United States

OCTOBER TERM, 1981

UNITED STATES OF AMERICA,
Petitioner,

vs.

GENERIX DRUG CORPORATION, ET AL.,
Respondents.

On Petition for Writ of Certiorari to The United States Court of Appeals For the Eleventh Circuit

OBJECTIONS TO MOTIONS FOR LEAVE TO FILE AMICUS CURIAE BRIEFS

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OBJECTIONS TO MOTIONS FOR LEAVE TO FILE AMICUS CURIAE BRIEFS

Respondents GENERIX DRUG CORP., LEWIS MICHAEL ORLOVE, GARY R. DUBIN and OFELIA PEREZ [referred to collectively as GENERIX] have received motions for leave to file amicus curiae briefs from four groups: The Proprietary Association; the Pharmaceutical Manufacturers Association [PMA]; the Generic Pharmaceutical Industry Association [GPIA] and Medicine in the Public Interest. GENERIX objects to two of the amicus briefs for the following reasons:[1]

1. The GPIA includes as members Bolar Pharmaceutical Co., Inc. and Zenith Laboratories, Inc. In its order on Motion for Preliminary Injunction, the district judge enjoined GENERIX from distributing all of its Goldline products which contain spironolactone and spironolactone with hydrochlorothiazide. GENERIX pointed out in its motion for rehearing that it distributes spironolactone and spironolactone with hydrochlorothiazide manufactured by Bolar and Zenith and that these products have received approval from the FDA on the basis of abbreviated new drug applications [ANDAs]. Nevertheless, the trial court denied GENERIX' motion for rehearing. Therefore, if the Fifth Circuit's decision is reversed and the trial court's order is reinstated, GENERIX will be prevented from distributing products manufactured by Bolar and Zenith.

2. In addition, the GOVERNMENT's position seems to be that it can require complete new drug applications

[1]GENERIX disagrees with the argument presented by the Proprietary Association, i.e., that over-the-counter drugs are not an issue in this case. It also disagrees with the substantive arguments presented by the PMA. However, GENERIX will respond to these arguments in its briefs on the merits. It does not object to the filing of these two amicus briefs.

[NDAs] under the statute, but that it may allow the filing of ANDAs as a matter of administrative convenience. Bolar and Zenith frequently obtain ANDAs for their products, not NDAs. Bolar's and Zenith's position is inconsistent with the GOVERNMENT's position to the extent that the GOVERNMENT seeks the authority to require NDAs for generic drugs. GENERIX submits that the brief filed by GPIA, which seems to endorse the GOVERNMENT's position in the case without qualification, does not truly reflect the interests of Bolar and Zenith.

3. GENERIX also objects to the brief filed by Medicine in the Public Interest because it relies extensively on unsubstantiated hearsay which is not a part of the record in this case. The GOVERNMENT produced evidence in this case that differences in bioavailability and bioequivalence between generic products and the brand names *may* present problems to patients using the generic products. However, the GOVERNMENT never introduced evidence that there were any differences between the GENERIX products and the brand name products. Therefore, there was no evidence that the GENERIX products were dangerous. The Medicine in the Public Interest brief attempts to overcome the lack of proof in this record by references to newspaper articles about a manslaughter trial of an Ohio pharmacist for allegedly dispensing unapproved generic furosemide. E.g., Brief at 11, 16. Although the pharmacist was acquitted, the brief claims that the

acquittal "does not detract from the fact that this unapproved drug caused or contributed to [the] death." There is no record evidence here substantiating this hearsay claim. GENERIX objects to this brief.[2]

[2]If this case were to turn on unsubstantiated hearsay reports from the news media, it would be possible for GENERIX to argue, for example, that pre-market approval does not eliminate possible health problems from drugs. GENERIX could rely on the recent program on 60 Minutes in which Mike Wallace disclosed that selacryn, a drug manufactured by Smith, Kline & French and presumably approved by the FDA, has caused the injuries or deaths of numerous persons. Such reliance would be improper. GENERIX believes that this case should be decided on the basis of the record presented in the district court.

CONCLUSION

WHEREFORE, for the reasons stated, GENERIX requests that the Motions for Leave to File Amicus Curiae Briefs filed by the Generic Pharmaceutical Industry Association and Medicine in the Public Interest be denied.

Respectfully submitted,

/s/_____

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April 21, 1982

Docket Sheet

NO. 81-1222-CFX	TITLE United States, Petitioner, v. Generix Drug Corporation, et al.

DOCKETED	COURT
Dec. 30, 1981	United States Court of Appeals for the Eleventh Circuit

DATE	PROCEEDINGS AND ORDERS
	Counsel for petitioner: Solicitor General
	Counsel for respondents: Roby Greene
Nov. 23, 1981	Application for an extension of time to file petition for writ of certiorari, and order granting same until Jan. 2, 1982, by White, J., Nov. 24, 1981.
Dec. 30, 1981	Petition for writ of certiorari filed.(Record filed)
Feb. 3, 1982	Brief for the respondents in opposition filed.
Feb. 10, 1982	DISTRIBUTED. 2-26.
Feb. 18, 1982	Reply memorandum for the U. S. filed. (D).
Mar. 1, 1982	Petition GRANTED.

Apr. 14, 1982	Suggestion of Mootness filed by respondents.
Apr. 14, 1982	Motion of Generic Pharmaceutical Industry Association, Inc. for leave to file a brief as amicus curiae filed.
Apr. 15, 1982	Joint appendix filed.
Apr. 15, 1982	Brief for petitioner filed.
Apr. 15, 1982	Motion of Medicine in the Public Interest for leave to file a brief as amicus curiae filed.
Apr. 15, 1982	Motion of The Proprietary Association for leave to file a brief as amicus curiae filed.
Apr. 15, 1982	Motion of Pharmaceutical Manufacturers Association for leave to file a brief as amicus curiae filed.
Apr. 20, 1982	DISTRIBUTED. 4-23. (Suggestion of mootness).
Apr. 22, 1982	Opposition of respondents to motions of Generic Pharmaceutical Industry Association, Inc., Medicine in the Public Interest, The Proprietary Association, and Pharmaceutical Manufacturers Assoction, for leave to file briefs as amicus curiae filed.
Apr. 26, 1982	The motion of Generic Pharmaceutical Industry Association for leave to file a brief as amicus curiae is GRANTED. The motion of Medicine in the Public Interest for leave to file a brief as amicus curiae is GRANTED. The motion of The Proprietary Association for leave to file a brief as amicus curiae is GRANTED. The motion of Pharmaceutical Manufacturers Association for leave to file a brief as amicus curiae is GRANTED.
	(Over)

81-1222

Title

No.

DATE	PROCEEDINGS AND ORDERS
Apr. 26, 1982	Brief for the U. S. in response to memorandum for respondent suggesting mootness filed.
Apr. 27, 1982	DISTRIBUTED. 4-30. (Suggestion of mootness by respondent
May 3, 1982	The respondents' suggestion of mootness is REJECTED.
May 3, 1982	Order extending time to file the respondents' brief on the merits until June 2, 1982.
June 4, 1982	Brief for respondents Generix Drug Corporation, et al. filed
Aug. 5, 1982	CIRCULATED.
Oct. 8, 1982	Reply brief for the U. S. filed. (D).
Nov. 3, 1982	ARGUED.